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Application of 9-phenyl-fluoren-9-yl Protected Amino Acids in the Synthesis of Tetrahydro-ß-Carbolines

Christopher Lood

Aalto University

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Application of 9-phenyl-fluoren-9-yl Protected Amino Acids in the Synthesis of Tetrahydro-ß-Carbolines

Christopher Lood

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Abstract

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Abstract

Tetrahydro-*ß*-carbolines are a prominent group of tricyclic natural products belonging to the indole alkaloids. The large diversity of complex polycyclic compounds in the family coupled with their medicinal properties has made them an extensively studied and extremely attractive target for synthetic organic chemists during the last decades. Reserpine, previously proscribed against hypertension, and tadalafil, a potent PDE5 inhibitor and currently one of the top grossing small molecule pharmaceuticals illustrates the importance of the compound class.

The asymmetric synthesis of tetrahydro-*ß*-carbolines traditionally relies on a few proven methodologies. The chirality has either been introduced diastereoselectively by substrate controlled reactions, using *e.g.* chiral auxiliaries, or by external asymmetric induction utilizing *e.g.* chiral catalysts. Our knowledge and experience on the use of amino acids as starting material in natural product synthesis prompted us to investigate the possibility of transferring the inherent chirality of amino acids to the tetrahydro-*ß*-carboline scaffold *via* a chiral pool approach. The use of amino acids as chiral starting material is however hampered by their propensity to undergo racemization/epimerization under certain reaction conditions. To this effect, the 9-phenyl-fluoren-9-yl protecting group was introduced as a means to both protect the amine functionality and at the same time also to protect the vulnerable stereocenter at the *alpha*-position on the amino acid derivatives.

This thesis aims to provide the reader with a short literature background on the chemistry of tetrahydro-*ß*-carbolines as well as an overview of different methods available to suppress racemization/epimerization of amino acid derived carbonyl compounds. The thesis will then culminate in the author's own work regarding the synthesis of the tetrahydro-*ß*-carboline natural products harmicine and eleagnine, by use of a chiral pool approach coupled with a 9-phenyl-fluoren-9-yl protecting group strategy. Herein is furthermore described the synthesis of chiral 2-indolyl methanamines, a structurally closely related group of compounds to the tetrahydro-*ß*-carbolines largely overlooked in the chemical literature. The thesis will finally end on a discussion regarding the mechanism behind the ability of the 9-phenyl-fluoren-9-yl amine protecting group to retain the stereochemical integrity of amino acid derived carbonyl compounds.

Keywords Amino acid, Protecting group, Natural product, Alkaloid, Total Synthesis

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-You can observe a lot by watching

Lawrence Peter “Yogi” Berra, American Baseball Player

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Espoo (Otaniemi), May 2015
Christopher Lood

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List of publications

This doctoral dissertation consists of a summary of the authors work and related literature and of the following publications, which from here on are referred to in the text by their Roman numerals.

I Lood, C. S.; Koskinen, A. M. P. *Chem. Heterocycl. Compd.* **2015**, *50*, 1367 – 1387; DOI: 10.1007/s10593-014-1602-4

II Lood, C. S.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2014**, 2357 – 2364; DOI: 10.1002/ejoc.201301903

III Lood, C. S.; Nieger, M.; Koskinen, A. M. P. *Tetrahedron* **2015**, Published Online (28 May 2015); DOI: 10.1016/j.tet.2015.05.063

IV Lood, C. S.; Laine, A. E.; Högnäsbacka, A.; Nieger, M.; Koskinen, A. M. P. *Eur. J. Org. Chem* **2015**, Published Online (1 may 2015); DOI: 10.1002/ejoc.201500391

Author's contribution

The author has contributed to the publications as stated below.

I The author wrote the article together with the co-author.

II The author designed and carried out the experimental work. The article was written together with the co-author.

III The author designed and carried out the experimental work. The crystallographic data was collected by co-author (M. N.). The article was written together with co-author (A. M. P. K), with the exception of the reporting of crystallographic parameters which was done by co-author (M. N.).

IV The author designed and carried out the experimental work together with co-author (A. E. L). Co-author (A. H.) prepared the (*R*)-enantiomer of **123a** under the guidance of the author. Co-author (A. E. L.) performed the DFT calculations. The author performed the MM calculations together with co-author (A. E. L.). All crystals, except for compound **129**, were grown by the author. The crystallographic data was collected by co-author (M. N.). The author interpreted the data and wrote the article together with co-author (A. M. P. K.), with the exception of the reporting of crystallographic parameters which was done by co-author (M. N.).

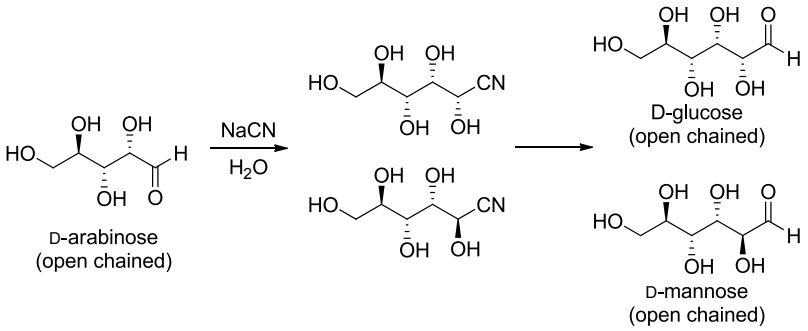
Abbreviations and symbols

*β*C	*β*-carboline
Ac	acetyl
All	allyl
Ar	aryl
B3LYP	Becke three parameter Lee-Yang-Parr
Bn	benzyl
BNR	Bischler-Napieralski reaction
Boc	*t*-butyloxycarbonyl
BOX	bis-oxazoline
CB_1	cannabinoid receptor type 1
CB_2	cannabinoid receptor type 2
Cbz	benzyloxycarbonyl
CTH	catalytic transfer hydrogenation
CIP	Cahn-Ingold-Prelog
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DH*β*C	dihydro-*β*-carboline
DIBAL-H	diisobutylaluminium hydride
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
de	diastereomeric excess
E	electrophile
ee	enantiomeric excess
Glc	glucose
GTP	guanosine-5'-triphosphate
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
Ipc	isopinocampheyl
IUPAC	international union of pure and applied chemistry
kcal	kilocalorie
KHMDS	potassium bis(trimethylsilyl)amide
kJ	kilo joule
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide

MM	molecular mechanics
NaHMDS	sodium bis(trimethylsilyl)amide
NMM	*N*-methylmorpholine
OPLS	optimized potential for liquid simulations
MMFF	Merck molecular force field
MOC	memory of chirality
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoramide)
NOESY	nuclear Overhauser effect spectroscopy
PDE5	phosphodiesterase type 5
Piv	pivaloyl
Pf	9-phenyl-fluoren-9-yl
Pg	protecting group
QM	quantum mechanics
rt	room temperature
STR	strictosidine synthase
T3P	propylphosphonic anhydride
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THβC	tetrahydro-β-carboline
THIQ	tetrahydroisoquinoline
THF	tetrahydrofuran
TMS	trimethylsilyl
Tr	trityl (triphenylmethyl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	tosyl (*p*-toluenesuflonyl)

1. Introduction

In organic chemistry one of the main challenges, and the cause of intense research from groups all around the globe, lie within asymmetric synthesis. Asymmetric synthesis/ induction is an old concept that can be traced back to the study by Emil Fischer in 1894 on the origin of the carbohydrate stereochemistry and the development of the Kiliani-Fischer synthesis (Scheme 1).[1,2,3] Although the apparent age of these groundbreaking ideas, this type of chemistry still leaves room for big improvements. During the years since, impressive achievements in the total synthesis of highly complex natural products have been the frontier in the development of new protocols for asymmetric transformations. Despite this fact, it still remains difficult to obtain complete enantiospecific control over reactions.



Scheme 1. Classic Kiliani-Fischer synthesis, homologation of D-arabinose to D-glucose and D-mannose

One strategy to synthesize chiral compounds is to pass on the stereochemical information to the end product by the use of chiral starting materials, from the so called "chiral pool". Nature, of course, the biggest supplier of chiral starting materials, provides us with a range of useful compounds, e.g. amino acids, sugars and terpenes, as single enantiomers in large quantities at an affordable price. The use of compounds from the chiral pool in synthetic organic chemistry is by no means a new strategy. Due to the obvious simplicity and the relative inexpensiveness of the starting material that the method offers in creating stereogenic centers it has been widely used in the synthesis of natural products and other compounds of medicinal and/or industrial importance.[4]

There are 23 proteinogenic amino acids (20 of which are encoded straight from the genome by triplet codons), however including the non-proteinogenic ones, the total number of naturally occurring amino acids is far higher. Many of these compounds contain at least one chiral center and are also commercially available in significant

quantities at a low price. More than that, the amino acids are, obvious by their nomenclature, equipped with at least two functional groups, which can be subjected to a huge number of synthetic manipulations, making them extremely versatile building blocks for a large range of chemical applications. However, the use of chiral amino acids in synthetic organic chemistry does suffer from some critical limitations, hampering their usability. The valuable synthetic intermediates of e.g. chiral *α*-amino-aldehydes, -ketones, -esters and amides derived from amino acids serve as illustrative examples (Figure 1). The acidity of the *α*-proton makes these compounds vulnerable towards racemization/epimerization and ultimately not suitable for carriers of stereogenic information under certain reaction conditions. Methods to overcome these specific limitations are therefore in great demand.

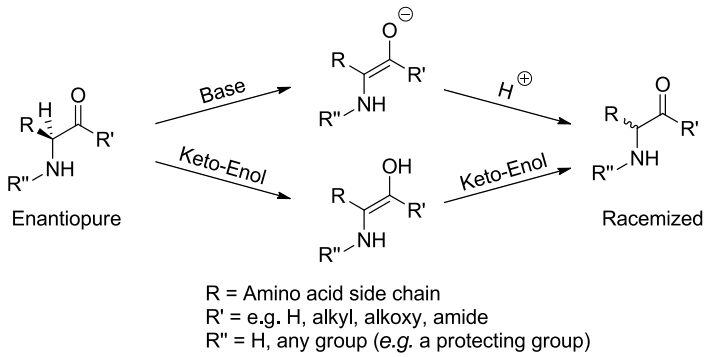


Figure 1. Racemization of *α*-amino carbonyl compounds *via* an enolization mechanism

In order to deal with the abovementioned racemization/epimerization issues, the 9-phenyl-fluoren-9-yl (Pf) group was introduced by Henry Rapoport, in 1985.[5,6] Rapoport originally utilized the strategy in the synthesis of (+)-apovincamine from asparagine, to regioselectively direct enolate formation away from the vulnerable stereocenter (described more detail in chapter 2.2.1). Rapoport also quickly realized the potential of such a protecting group, expanding the scope to show that *N*-Pf *α*-amino aldehydes were configurationally stable,[7] and also started to routinely incorporate the strategy in various synthetic endeavours.[8] Many former students of Rapoport's subsequently picked up on the concept, after leaving his research team to pursue their own careers, and the Pf-protecting group consequently made its journey from sunny Berkeley California to cold Espoo Finland, finally ending up in my humble hands.

This dissertation describes the use of the Pf-protecting group in the synthesis of tetrahydro-*β*-carbolines (TH*β*Cs), a prominent family of indole alkaloids, starting from amino acids.[9] Examples from this family include tryptoline which makes up the basic

structural skeleton of the THβCs, the natural products sarpagine, vincamine and ajmalicine, the antihypertensive agent reserpine,[10] the antiviral compound eudistomin C[11] and the synthetic THβC tadalafil,[12] a powerful PDE5 inhibitor and block buster pharmaceutical (Figure 2A). The following discussion will focus on the transfer of the chiral center present in the starting amino acids, to the C-1 position of the THβC C-ring (Figure 2B). The Pf-group is employed within this work to ensure complete configurational stability of the amino acid derivatives. The first chapters consist of a condensed literature overview of Pf-protecting group chemistry, including some selected applications, as well as a look into the world of THβCs. The discussion will then proceed to include a summary of the chemistry developed within the framework of this thesis, starting with the synthesis of harmicine,[I,II] eleagnine[III] and chiral 2-indolyl amines[IV] and ending on a discussion regarding the mechanism of the Pf-protecting groups ability to maintain the configurational stability of chiral α-amino carbonyl compounds[IV].

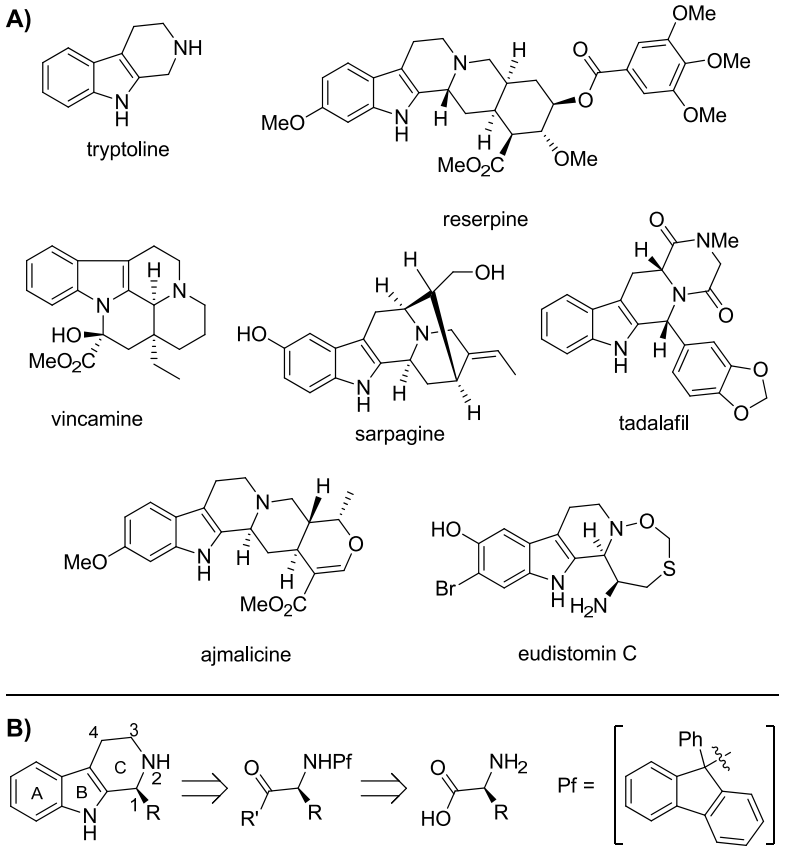
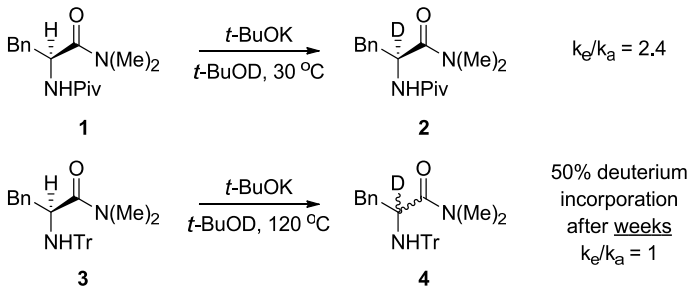


Figure 2. A) Representative examples of THβCs. B) Fundamental principle discussed within the framework of this dissertation. R = amino acid side chain.

2. The 9-phenyl-fluoren-9-yl protecting group in organic synthesis

2.1. Properties of the Pf-protecting group

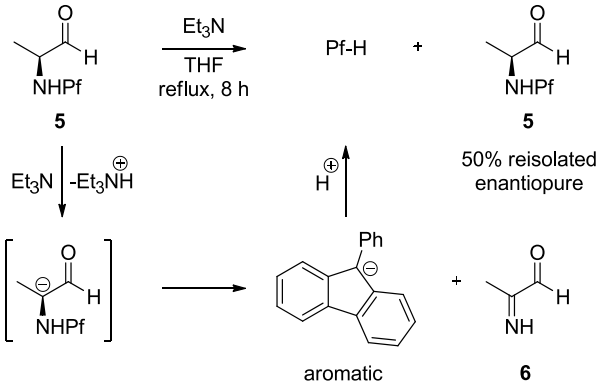
The story begins in 1981 with Guthrie's seminal study on the trityl (Tr) group and its ability to maintain the stereochemical integrity of phenylalanine dimethylamide derivative under harsh basic conditions.[13] Guthrie observed that when treating *N*-pivalylphenylalanine dimethylamide **1** with *t*-BuOK in *t*-BuOD, the rate of proton/deuterium exchange was greater than the rate of racemization (Scheme 2). An early example of the phenomenon that today would be described as memory of chirality (MOC), a concept coined[14] in 1991 and coeval with one of the earliest published examples by Seebach.[15] Speculating on the role of the steric bulk of the *N*-substituent, they synthesized compound **3** and subsequently submitted the substrate to the same racemizing reaction conditions. They found that, even at elevated temperature, the proton/deuterium exchange was slowed down to an almost complete stop. After keeping the reaction going for weeks at 120 °C, only 50% deuterium incorporation could be observed. Also, despite the extra bulk introduced to the phenylalanine substrate, no stereospecifity in the proton/deuterium exchange was detected.



Scheme 2. Stereospecifity of proton/deuterium exchange in **1** and **2**; k_e = rate constant of proton/deuterium exchange; k_a = rate constant of loss of optical activity.

Later the concept was picked up by Rapoport during his synthetic studies on (+)-apovincamine. (Chapter 2.2.1). Rapoport however found that the corresponding *N*-Tr-compounds were too labile towards acidic solvolysis, *e.g.* during silica gel chromatography, to be of practical use. Instead he introduced the idea of using the analogous Pf-group as an amine protecting group. Pf-Cl was known to be 6000 times less reactive than Tr-Cl in solvolysis studies.[16] The increased acid stability can be accredited to the lower stability of the Pf-carbenium ion due to its antiaromatic character.[17] Rapoport also went on to synthesize *N*-Pf-L-alaninal **5**, and proving it to be configurationally stable

towards basic conditions as well as towards silica gel chromatography.[7] Rapoport noted that when refluxing aldehyde **5** in THF for 8 h together with 100 mol-% Et_3N, 50% of the starting material decomposed (Scheme 3). Investigation of the reaction mixture showed the other major reaction component to be 9-phenylfluorene, indicating a base induced elimination reaction of a 9-phenylfluoren-9-yl anion. Investigation of the remaining 50% of starting material showed no degradation in the enantiopurity. Based on these observations Rapoport came to the conclusion that the base induced elimination reaction must be faster than the corresponding deprotonation/reprotonation reaction that would cause racemization. The corresponding elimination reaction of *e.g.* compound **3** could however be considered unlikely due to the large difference in the pK_a values of Tr-H (pK_a 31.5)[18] and Pf-H (pK_a 18.5)[19] which is due to the aromatic nature of the 9-phenylfluoren-9-yl anion.

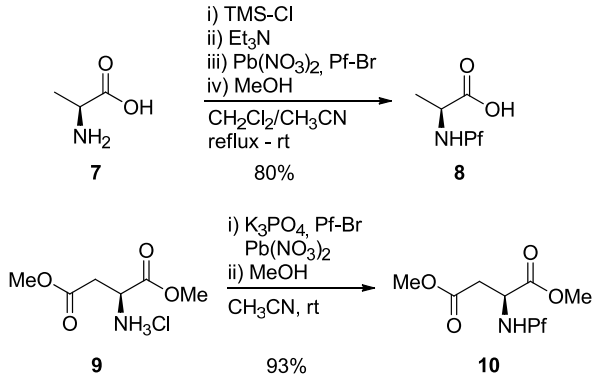


Scheme 3. Base induced elimination of 9-phenylfluoren-9-yl anion from aldehyde **5**

The introduction of the Pf-group onto an amino acid derivative is fairly straightforward and high yields can routinely be achieved.[20] Pf-Br, which is commercially available albeit at a rather hefty price, is used as the Pf-source. Alternatively, Pf-Br can easily be synthesized in large scales, using a two-step procedure from fluorenone.[21] Typical conditions for the 9-phenylfluoren-9-ylations involve treating the amino acid with Pf-Br in the presence of a base and $Pb(NO_3)_2$ as a bromide scavenger (Scheme 4). If there are free hydroxyl groups, including carboxylic acids, present on the substrate, an *in situ* protection as the TMS ether, or ester, might be called for, as is exemplified by the Pf-protection of alanine **7** (Scheme 4). The removal of the Pf-group can easily be accomplished under both hydrogenolysis[22] and acidic solvolysis[23].

There have been some speculations to how the Pf-group is able to so effectively shield the α-carbon on α-amino acid derivatives from racemization. Except for the obvious steric

shielding that the Pf-group imposes, it has also been put forth that stereoelectronic effects might play a role for the unprecedented configurational stability exhibited by these substrate. Molecular mechanics (MM) calculations have shown the H_α to be antiperiplanar or alternatively periplanar to the carbonyl C=O bond. [24] Such a conformation would effectively minimize the interaction between the C-H_α σ-orbital and the C=O π*-orbital, leading to a lowering of the H_α acidity. This theory has indeed found some support in crystallographic measurements. [25, 26] However, until now no comprehensive investigations had been undertaken which will be discussed further in chapter 4.[IV]



Scheme 4. 9-phenylfluoren-9-ylation of alanine and dimethyl aspartate

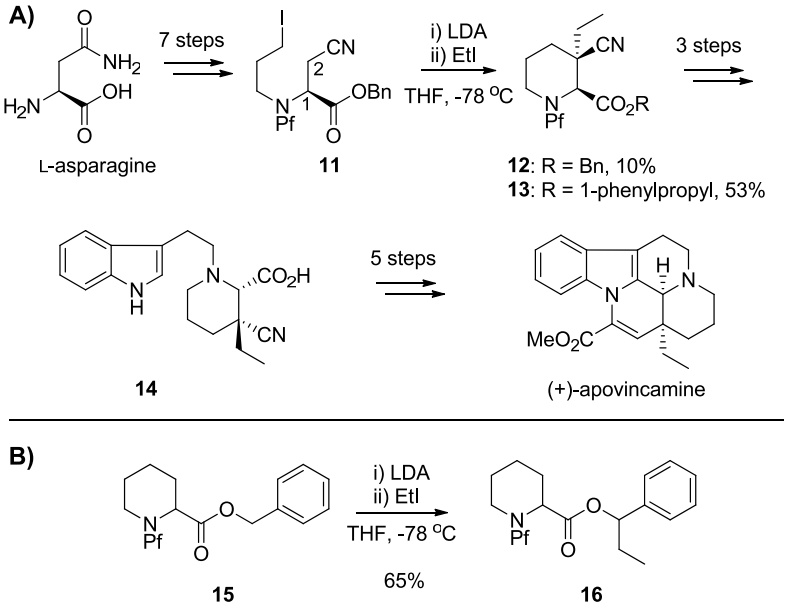
2.2. Notable examples in synthesis

There exist quite a number of total synthesis of natural products employing a Pf-protecting group strategy and below will follow some successful applications of the Pf-protecting group in natural product synthesis. Three such cases will be presented in more detail. Additional examples include, *e.g.* the total synthesis of polytheonamide B,[27] (-)-kainic acid,[28] different anisomycin derivatives,[29] (+)-vincamine,[30] ribasine,[31] microcystin LA[32] and *homo*-sphingosine.[26]

2.2.1. Total synthesis of (+)-apovincamine

The pioneering study on the use of the Pf-group as an *N*-protecting group in total synthesis was performed by Henry Rapoport in 1985 during his synthetic studies on the THβC apovincamine, a monoterpenoid alkaloid belonging to the *Aspidosperma* class of

indole alkaloids (Scheme 5A).[5,33] The synthesis started with the synthesis of iodide **11**, which was straightforwardly prepared from L-asparagine in 7 steps. Next, in the key



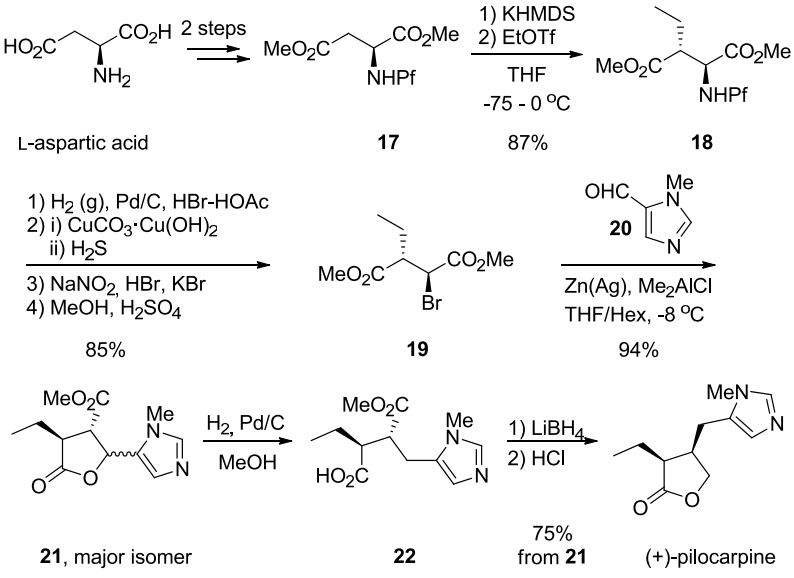
Scheme 5. A) The Pf-protecting group in the synthesis of (+)-apovincamine from L-aspargine. B) Regioselectivity in the treatment of **15** with LDA and EtI

reaction step they aimed to ring close iodide **11** to the corresponding pipecolate, *via* chemoselective enolization of the C-2 position without risking racemization /epimerization at C-1. Based on the knowledge regarding the ability of the Tr-group to suppress proton/deuterium exchange in phenyl alanine derivative **3** to almost a complete stop (*vide supra*) they opted to try the reaction using the more stable and similar sized Pf-group. To their delight, when treating compound **11** with an excess of LDA in the presence of EtI they obtained a mixture of **12** and **13**, with full retention of the C-1 stereochemistry and complete stereocontrol at C-2 in the introduction of the ethyl group. The stereocontrol at C-2 could be attributed to the rigid piperidine ring structure, wherein the benzyl ester group is occupying an axial position, due to the bulkiness of the equatorial Pf-group, leading to the highly selective alkylation. It is interesting to note that the benzyl ester present in the substrate was also alkylated to a significant degree. They also found the same mode of reactivity when treating pipecolate **15** with LDA and quenching the reaction with EtI, to give compound **16** in a moderate 65% yield (Scheme 5B). This reaction really showcases the Pf-protecting group's potential to block the C-1 position from enolization, but also serves to illustrate that rather unique regioselectivities

can be achieved by employing this type of chemistry. The total synthesis was then completed by forming the TH*β*C ring scaffold *via* a phenylphosphonic dichloride mediated decarbonylation, substitution of the indole *N*-H with methyl bromoacetate followed by a Dieckmann condensation and finally ketone reduction/dehydration affording (+)-apovincamine.

2.2.2. Total synthesis of (+)-pilocarpine

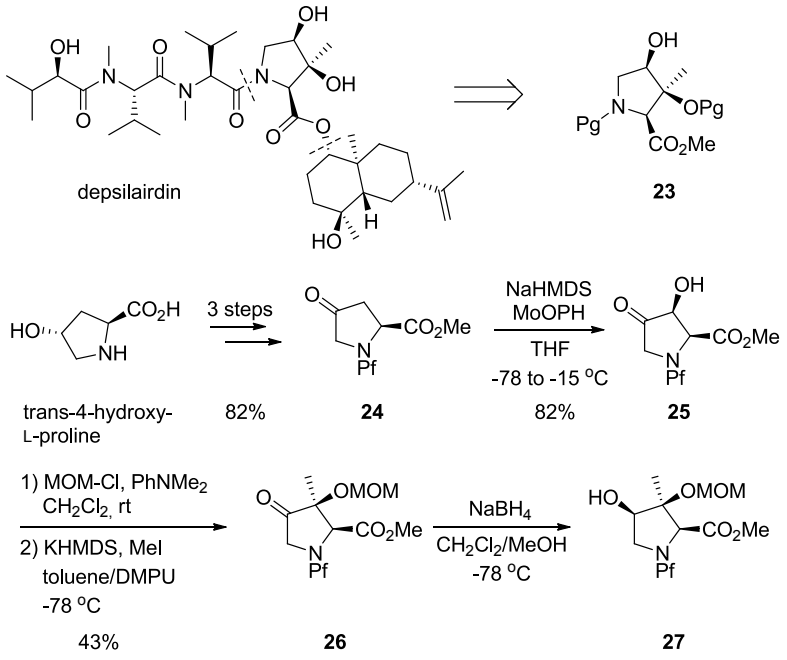
Next we have yet another total synthesis by Rapoport, *i.e.* the total synthesis of (+)-pilocarpine (Scheme 6).[34] The synthesis started from L-aspartic acid, which was esterified and *N*-Pf protected to diester **17**. One of the key steps, the diastereoselective alkylation of **17** with ethyl triflate was then performed. Very high selectivity was achieved (18:1), and batches of up to 60 g of starting material could be run without any problems, show casing once again the Pf-groups capability of regioselectively directing the enolization. Next, the amino acid nitrogen was substituted with a bromide, to give bromo ester **19**, *via* a four step reaction sequence consisting of hydrogenolysis, selective ester hydrolysis, diazotization in the presence of HBr/KBr and finally Fischer esterification. A Reformatsky reaction between bromo ester **19** and aldehyde **20,** mediated by Zn(Ag) together with Me_2AlCl, gave lactone **21** as the major isomer, in good selectivity. Lastly, lactone **21** was transformed into (+)-pilocarpine after hydrogenolysis and ester reduction/lactonization.



Scheme 6. Total synthesis of (+)-pilocarpine from L-aspartic acid

2.2.3. Total synthesis of despilairind, preparation of a dihydroxy methyl proline fragment

Lastly we have the total synthesis of despilairdin (Scheme 7), a more recent example by Ward and co-workers, in which a dihydroxy methyl proline fragment **23** was prepared by Pf-protecting group chemistry.[35] First, trans-4-hydroxy-L-proline was subjected to Fischer esterification, 9-phenyl-fluoren-9-ylation and Swern oxidation to give ketone **24** according to Sardina's studies on polyhydroxylated pyrrolidones.[36] The sodium enolate of ketone **24**, regioselectively controlled by the aid of the Pf-group, was then treated with Vedejs' reagent to give hydroxyl ketone **25** as a single diastereomer. MOM-protection of the hydroxyl group followed by methylation gave ketone **26**, as the major diastereomer, due to the pseudo equatorial alignment of the methyl ester group in the potassium enolate.[37] $NaBH_4$ reduction of ketone **26** furnished the dihydroxy methyl proline fragment **27**, corresponding to building block **23**, to be used in the total synthesis of depsilairdin.



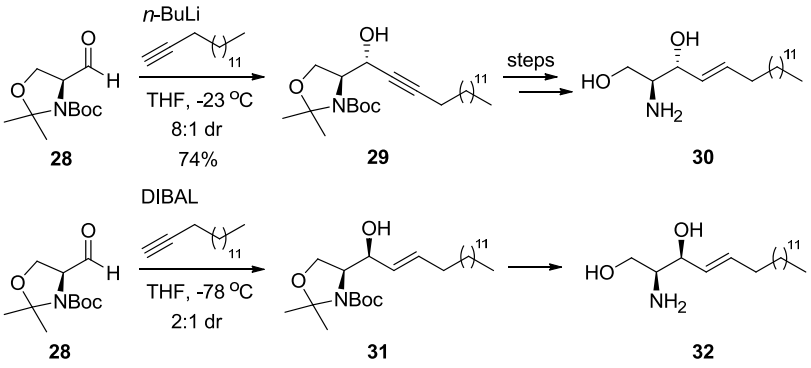
Scheme 7. Total synthesis of depsilairdin, synthesis of fragment **27** (corresponding to fragment **23**); Pg = protecting group

2.3. Alternative ways of combating racemization in amino acid derived compounds

The racemization sensitivity of α-amino carbonyl compounds is, and has been, a well-known problem.[38] As a consequence several methods addressing this dilemma, apart from the use of Tr- or Pf-protecting group chemistry, exist in the chemical literature. Some of these methods will be described below.

2.3.1. Garner's aldehyde

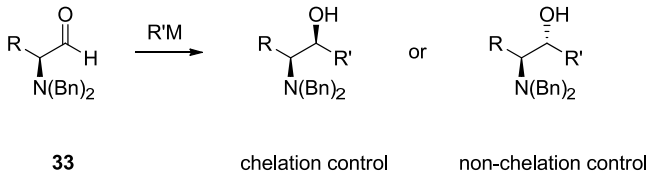
It would almost be considered as sacrilegious to not address the case of Garner's aldehyde when discussing the topic of natural product synthesis utilizing amino acids.[39] Garner's aldehyde **28** was introduced by Philip Garner in 1984. It is a fully protected serine derivative, configurationally stable (to purification on silica gel, vacuum distillation and during prolonged storage) building block that has found tremendous use in organic synthesis,[40] especially in the synthesis of sphingolipids, as illustrated by one of Garner's pioneering studies on sphingosine (Scheme 8). In his study, Garner's aldehyde was treated with lithiated 1-pentadecyne. Predominant *Re*-face attack furnished amino alcohol **29**, which after partial reduction of the triple bond and protecting group removal gave D-*erythro*-sphingosine **30** in a very straight forward manner. Garner also found that he could achieve reversal of the diastereoselectivity by treating Garner's aldehyde **28** by using the trans-vinylalane, derived from hydroalumination of 1-pentadecyne using DIBAL.[41] After protecting group removal D-*threo*-sphingosine **32** was accordingly obtained.



Scheme 8. Garner's sphingosine synthesis

2.3.2. *N,N*-dibenzylamino aldehydes

The use of *N,N*-dibenzylamino aldehydes **33** were popularized by Manfred Reetz in the late 1980's. [42] Their introduction was advertised as a general fix to ensure configurationally stability in combination with high stereoselectivity in both chelation controlled and non-chelation controlled addition reactions - depending on the choice of nucleophile (Scheme 9).[43] However, the claimed configurational stability was not to be considered general. Storage of the derivatives for prolonged periods of time, as well as subjecting the compounds to acids or bases could lead to degradation of the enantiopurity. In fact, silica gel chromatography was shown to completely racemize a phenyl alanine derived *N,N*-dibenzylamino aldehyde. [44] Hence, a certain measure of care must be undertaken in order to successfully use these types of derivatives, and in general the compounds are best used freshly prepared as crude materials.

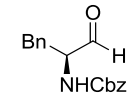
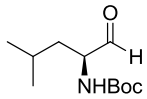
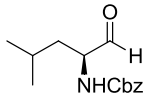
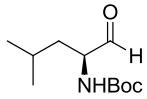
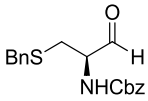
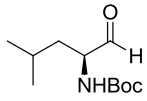


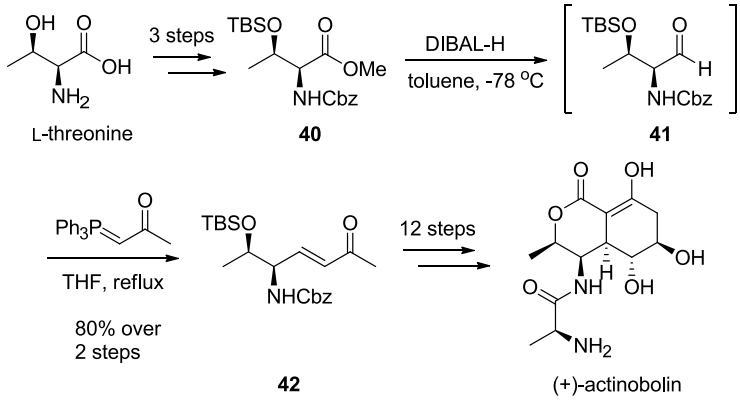
Scheme 9. Chelation versus non-chelation control in organometallic addition reactions to a generalized *N,N*-dibenzylamino aldehyde **33**

2.3.3. *N*-carbamate protected *α*-amino aldehydes

Carbamate protected *α*-amino aldehydes, although attractive synthetic intermediates are notoriously prone to racemization (Table 1).[45,46] Despite this generally accepted fact, these compounds can and have found uses. The trick is obviously once again to avoid excessive purification and prolonged storage at elevated or even ambient temperatures. The total synthesis of (+)-actinobolin serves as an illustrative example (Scheme 10).[47] Methyl ester **40** was first synthesized from L-threonine in 3 steps. DIBAL-H reduction of ester **40**, followed by an aqueous work up furnished aldehyde **41**, which was then immediately reacted further to enone **42** *via* a Wittig reaction. It was found to be necessary, owing to the aforementioned issues, to telescope the DIBAL reduction/Wittig reaction thereby avoiding epimerization issues of **41** upon silica gel purification. A 12 step sequence then transformed enone **42** into actinobolin.

Table 1. Configurational stability of carbamate protected α-amino aldehydes towards silica gel and prolonged storage[45,46]

During subjection to SiO_2			During Storage			
Compound	Degree of Racemization		Compound	Time	Temp	Ratio
	6 h	22 h		[Days]	[°C]	L/D
 **34**	53%	85%	 **37**	1	-30	99/1
 **35**	32%	65%	 **38**	9	-30	99/1
 **36**	99%	100%	 **39**	9	+24	7/3

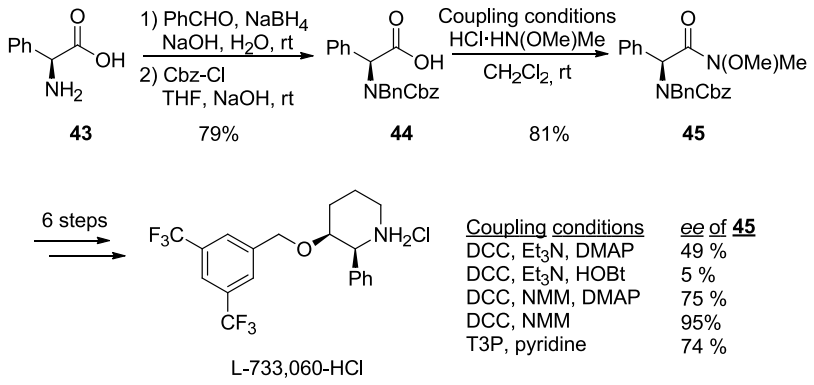


Scheme 10. Total synthesis of (+)-actinobolin

2.3.4. Reagent control

The last example presented involves the rather obvious way of applying a case to case trial and error approach. In the world of peptide synthesis, *i.e.* amide bond formation, such examples are plentiful. In fact, a large amount of coupling reagents and additives has been developed for the purpose of suppressing racemization along the course of the

reactions.[38b] Also, a range of screening methods, in order to evaluate and compare different reaction conditions used in amide couplings reactions, was developed early on.[48] The effect of a judicious choice of reagents and its influence on enantiopurity, was very well illustrated in the synthesis of 3-piperidinols from our laboratory when Weinreb amide **45** was targeted as a key building block (Scheme 11).[49,50] Fully protecting L-phenylglycine **43** as the corresponding *N,N*-benzylbenzyloxycarbonyl compound **44** was easily accomplished by a telescoped reaction sequence. Next the Weinreb amide formation was investigated. The best result was obtained by employing dicyclohexylcarbodiimide (DCC) in combination with *N*-methylmorpholine (NMM) (pK_{aH} 7.38) giving an *ee* of 95%, a quite impressive feat when taking into account the extreme configurational lability of phenylglycine derivatives.[51] Use of a stronger base, Et_3N (pK_{aH} 10.75) with standard additives such as dimethylaminopyridine (DMAP) or hydroxybenzotriazole (HOBt) caused significant amounts of racemization. Also, adding DMAP together with the DCC/NMM procedure proved detrimental. Using a more recently developed methodology, employing the coupling reagent propylphosphonic anhydride (T3P®) in combination with pyridine also racemized the substrate significantly.[52] The synthesis proceeded from amide **45** to provide the neurokinin 1 (NK-1) inhibitor L-733,060 in 6 steps.[53]



Scheme 11. Synthesis of L-733,060-HCl *via* Weinreb amide **45**

3. Tetrahydro-*β*-carbolines

TH*β*Cs, the C-ring saturated analogues of *β*-carbolines (*β*Cs) (for atom numbering and ring assignment, see Figure 2), which in itself is a subgroup of the indole alkaloids, comprise a vast amount of compounds. Of special importance are the chiral C-1 substituted TH*β*Cs alkaloids, a prominent collection of natural products containing *e.g.* the corynantheine, yohimbine and eburnamine-vincamine types of monoterpenoid alkaloids.[54,55,56] Also a large amount of more structurally simple alkaloids, denoted as "simple TH*β*Cs", can also be found within the TH*β*C family, examples include harmicine, trypargine, borrerine and eleagnine (Figure 3).[57] The following chapter will highlight some of the different methodologies that have successfully been applied in the asymmetric synthesis of TH*β*Cs, leading up to the presentation of the authors own research results. The literature review presented below does not aim to cover the entire research field, but instead aims to offer insight into the most important methodologies, emphasized with selected examples.

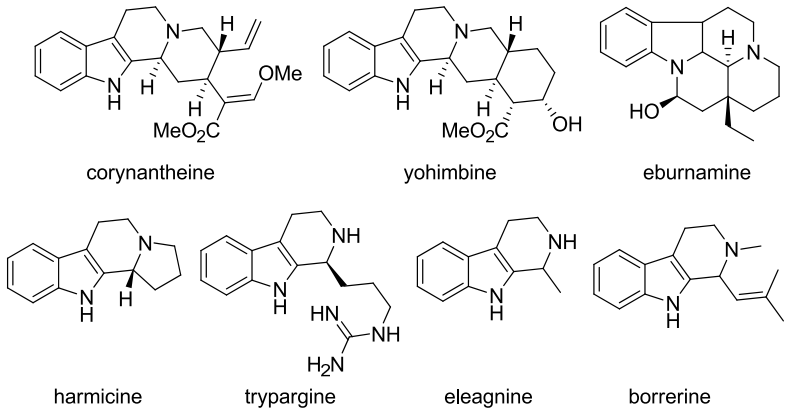


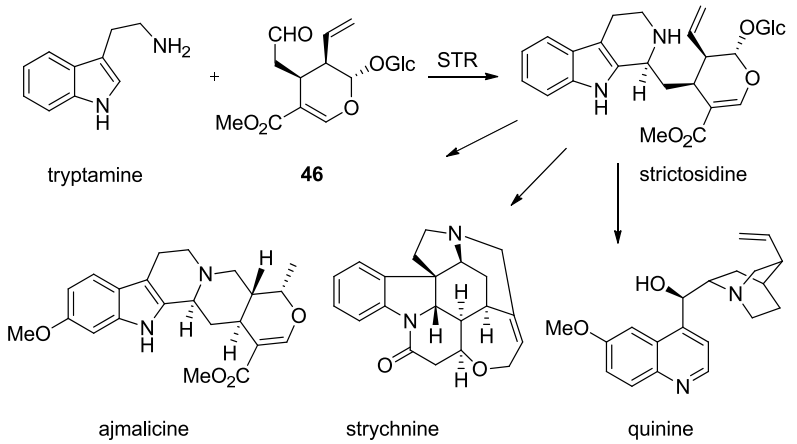
Figure 3. Monoterpeniod alkaloid subtypes (corynantheine, yohimbine and eburnamine) as well as examples of some of the simple TH*β*C (harmicine, trypargine, eleagnine and borrerine)

3.1. Synthetic methodologies towards TH*β*Cs

3.1.1. Biosynthesis

The biosynthesis of TH*β*Cs relies on the condensation reaction between a tryptamine and an aldehyde, to form the tricyclic ring structure. This reaction was first discovered in 1911, during explorations on the synthesis of tetrahydroisoquinolines (THIQs). The reaction was subsequently named the Pictet-Spengler reaction (PSR) after its inventors.[58]

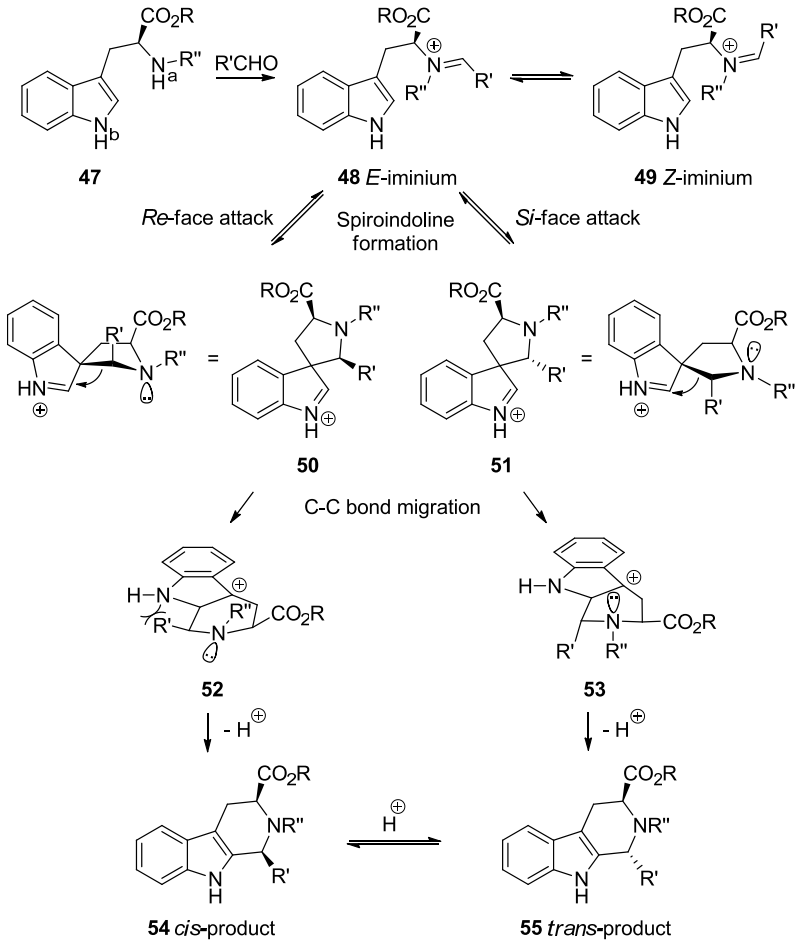
Much later, in 1977, the first Pictet-Spenglerase, strictosidine synthase (STR), was discovered in nature, a discovery that culminated in the elucidation of the biosynthetic pathway of the monoterpeniod alkaloid ajmalicine.[59, 60, 61] It was shown that STR efficiently catalyzed the reaction between tryptamine and secologanin **46** to give strictosidine (Scheme 12). Strictosidine is then the starting point in the biosynthesis for a large array of THβC (including *e.g.* reserpine). It is also the starting point for a number of other alkaloids, such as the famous *Strychnos* alkaloid strychnine; and the quinoline alkaloid quinine. The existence of Pictet-Spenglerases has obviously exploited in asymmetric synthesis and the scope of the enzymatic reaction has been extended to allow different tryptamines and aldehydes to be used as substrates.[60,62]



Scheme 12. STR catalyzed PSR of tryptamine and secolaganin **46**; Glc = glucose

3.1.2. Pictet-Spengler reaction

Arguably the most important way of synthesizing THβCs has historically been *via* the PSR. Tremendous progress has been made over the years since Pictet and Spengler's original synthesis of THIQs. The most important developments being the extension from the use of phenethylamines to include tryptamines and the introduction of non-aqueous conditions, subsequently leading to the diastereoselective PSR by using chiral tryptophan derivatives as the amine condensation partner.[60, 63] The mechanism of the diastereoselective PSR is a complicated, but interesting one. Essentially most changes to the reaction conditions have an impact on the selectivity outcome, *e.g.* acidic versus aprotic conditions, the size and electronic effect of the N_a (if any) substituent, the size and electronic effect of the tryptophan ester group and the size and electronic effect on the electrophile. However, as a broad generalization, as the studies of Cook has shown, trans selectivity, *i.e.* trans between the tryptophan ester group and the emerging C-1 substituent,

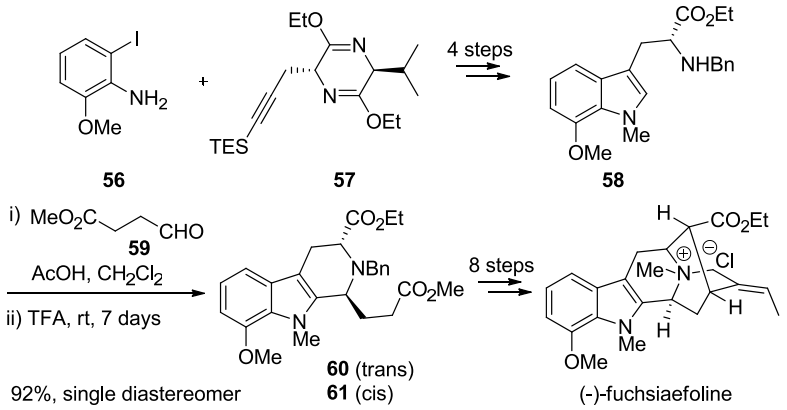


Scheme 13. Diastereoselective PSR mechanism

is far easier to achieve than cis.[64] But, as one might also expect, there are examples in the literature of highly cis selective PSRs, developed most extensively by Bailey.[65] However, things are further complicated by the fact that THβC tend to epimerize at the C-1 position under acidic conditions, towards the more thermodynamically stable product, which in most cases tends to be the trans isomer.[64] The generally accepted reaction mechanism can be rationalized accordingly (Scheme 13). First up is the question of the *Z* vs *E*-iminium intermediate. The *E*-iminium **48** is assumed to be lower in energy due to the unfavorable interaction, present in the **49** *Z*-iminium, between the indole ring and the R' group in the transition state leading up to the spiroindolenine formation. Cyclization of the *E*-iminium is then most likely to occur from the iminium *Si*-face, in this case due to the stereoelectronically favorable antiperiplanar alignment of the electron withdrawing ester

group. Also, the intermediate spiroindoline resulting from *Re*-face, having all the substituents in a syn fashion, is more sterically congested. After C-C bond migration to furnish the carbenium intermediates **52** and **53**, it is once again obvious that the intermediate resulting from the *Si*-face attack is lower in energy, because of the $A^{1,2}$ strain between N_b and R'. Aromatization then leads to the corresponding cis and trans THβC.

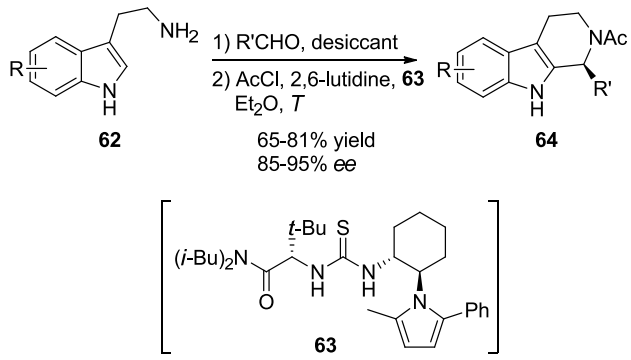
The diastereoselective PSR has been used on multiple occasions in the synthesis of THβC natural products. One of many example of this approach is the total synthesis of (-)-fuchsiaefoline by Cook (Scheme 14).[66] The non-commercially available D-tryptophan **58** was prepared *via* first a Larock[67] indolization reaction between aniline **56** and the by the Schöllkopf[68] amino acid synthesis method derived alkyne **57** followed by methylation of the indole nitrogen, removal of the chiral auxiliary and *N*-benzylation. PSR between tryptophan **58** and aldehyde **59** furnished THβCs **60** and **61**, in a 2:1 (trans:cis) dr. Acidic equilibration, of the diastereomeric mixture with TFA, furnished the trans adduct **60** as a single isomer, which was then taken further to give (-)-fuchsiaefoline.



Scheme 14. Cook's total synthesis of (-)-fuchsiaefoline

A long standing problem with the PSR has been the lack of enantioselective protocols. The first enantioselective PSR was reported by Nakagawa in 1996.[69] He used stoichiometric amounts of the chiral Lewis acid (+)-diisopinocampheylchloroborane ((+)Ipc_2BCl), together with *N*-hydroxytryptamines and some different aliphatic and aromatic aldehydes. The yields were in most cases good; however the enantioselectivities were at best only moderate. The development then proceeded further leading up to the first truly catalytic asymmetric PSR (acyl PSR) which was reported in 2004 by Jacobsen.[70] Jacobsen successfully employed a thiourea based organocatalyst **63** in the condensation between different tryptamines **62** and various aldehydes (Scheme 15), obtaining a small library of THβCs, generally in good yields with good enantioselectivity.

This achievement was soon followed by other organocatalytic examples reported by List[71] and Hiemstra,[72] both using chiral phosphoric Brønstedt acids.

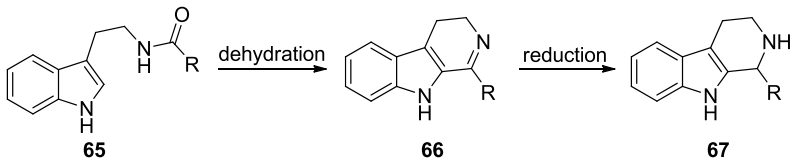


Scheme 15. Jacobsen thiourea catalyzed acyl PSR. R = H, 5-MeO, 6-MeO; R' = $CH(CH_2CH_3)_2$, $CH(CH_3)_2$, *n*-C_5H_{11}, $CH_2CH(CH_3)_2$, CH_2CH_2OTBS

Other examples of modifications to the PSR reaction, such as the use of chiral *N*-auxiliaries and the condensation of tryptamines with chiral aldehydes have also been developed.[73,74] In particular the synthesis of eudistomin C (Figure 2A), using Garner's aldehyde (*vide supra*), as the directing group is worth mentioning in this context.[74a] However, conceptually these different approaches do not differ much from the examples already presented and will therefore not be discussed in any more detail.

3.1.3. Bischler-Napieralski reaction

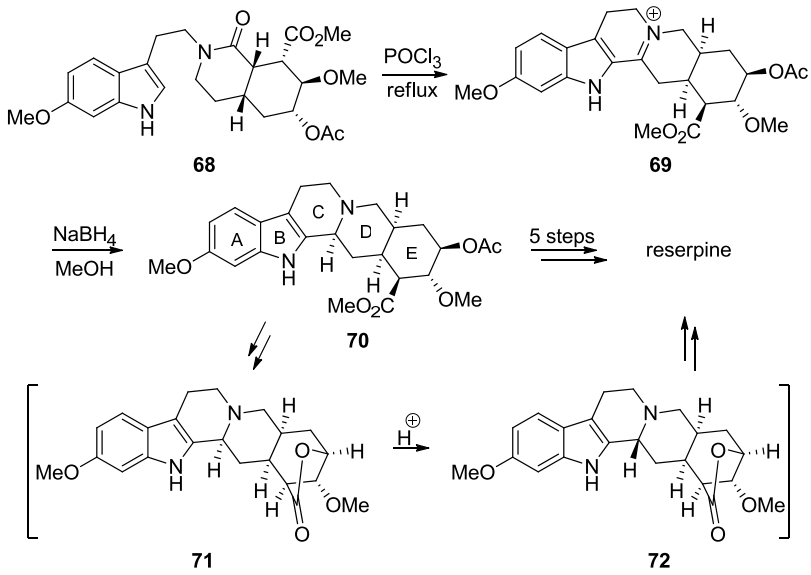
Another old reaction that has found extensive use in TH*β*C (and THIQ for that matter) synthesis is the Bischler-Napieralski reaction (BNR), discover in 1893.[75] The methodology found great use in the early days of alkaloid chemistry, and still today enjoys a privileged position as an attractive way of making complex natural products. The reaction in its simplest form is the ring closure of the generalized tryptophan amide **65** to



Scheme 16. Generic BNR of amide **65**

give a 3,4-dihydro-*β*-carboline (DH*β*C) **66**, by use of a dehydrating reagent such as $POCl_3$, PCl_5, $ZnCl_2$, $SOCl_2$ or $AlCl_3$. The resulting DH*β*C can then be reduced under various conditions to give the corresponding TH*β*C **67**.[76]

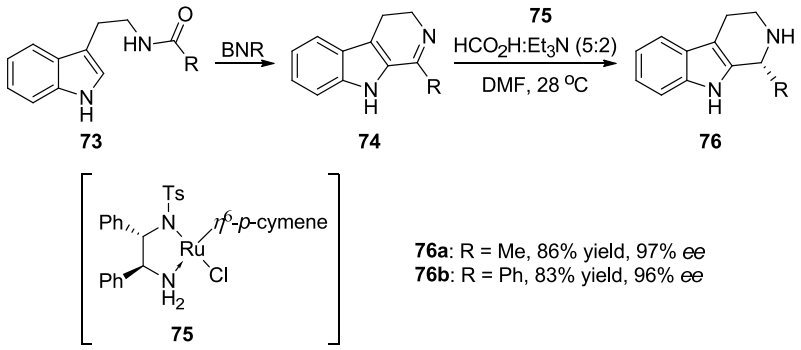
In the now classic total synthesis of reserpine, Woodward utilized the Bischler-Napieralski reaction on an advanced intermediate **68** which was dehydrated using $POCl_3$ to give DH*β*C **69** (Scheme 17). $NaBH_4$ reduction, with the hydride addition occurring from the opposite face of the trans decalin ring structure gave the expected TH*β*C **70**, with the wrong configuration at the TH*β*C C-1. As it happens, **70** is not only the kinetic product originating from the $NaBH_4$ reduction but it is also the more thermodynamically stable TH*β*C diastereomer, so simple acidic equilibration, *via* epimerization of the TH*β*C (*vide supra*), does not lead to the correct product. This is due to the substituents all being equatorial on ring E in the most energetically favorable conformation of **70**. Inverting the C-1 stereochemistry would inadvertently place the E-ring substituents in an axial position, causing a more strained system. However by tethering the E ring as lactone **71**, Woodward could shift the equilibrium. By treating lactone **71** with acid some of the forced strain within the molecule was relieved by flipping the indole ring segment away from the D/E-ring system leading to a more stable lactone **72**, having the correct C-1 stereochemistry. Simple lactone ring opening, using NaOMe, and introduction of the 3,4,5-trimethoxy benzoic acid then gave reserpine.[77] Woodward's synthesis of reserpine



Scheme 17. Woodward's total synthesis of reserpine

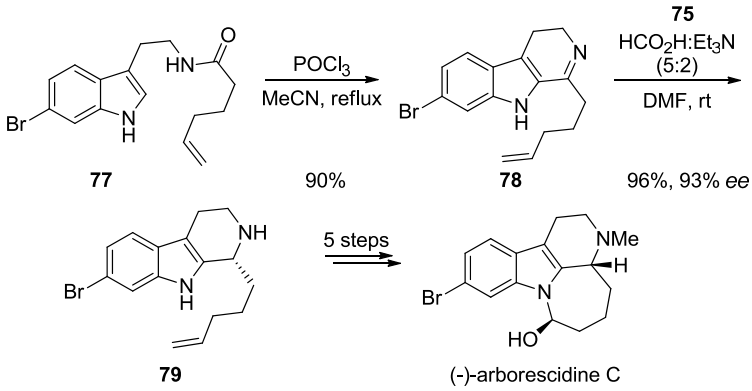
wherein internal asymmetric induction dictates the C-1 stereochemical outcome will serve to illustrate an example of diastereocontrol in the BNR/reduction synthesis of THβC.

With the introduction of catalytic asymmetric reduction reaction relying on external induction, in the form of chiral ligands, chemists soon found a way to combine the old (BNR) with the new (catalytic asymmetric hydrogenation). The first one to extend the new technology towards the THβC was Noyori (Scheme 18).[78] The DHβCs **74**, synthesized by the BNR from amides **73**, was subjected to asymmetric reduction under catalytic transfer hydrogenation (CTH) conditions, catalyzed by chiral Ru(II) catalyst **75**, to give THβC **76** in good yields and excellent enantioselectivity. Only two examples of THβCs were included in this first preliminary study and when scaling up the procedure to a 20 mmol scale, **76a** was obtained in good yield but with a slightly diminished *ee* of 93%, in comparison to the 97% *ee* obtained on a 1 mmol scale. The drop in *ee* could most likely be attributed to the lowering of the catalyst loading, extending the reaction time to 12 hours, inducing acid-catalyzed racemization of the THβC **76a** *vide supra* under the slightly acidic reaction conditions.



Scheme 18. Noyori's asymmetric CTH of DHβCs. Ts = tosyl

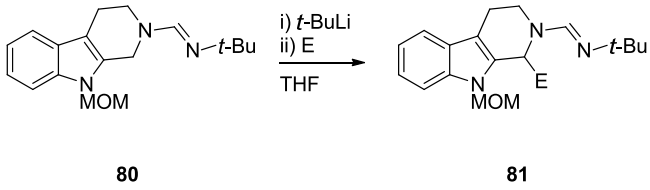
As a final example of the BNR approach, an example of the Noyori protocol in the synthesis of natural products is given, *i.e.* the synthesis of (-)-arborescidine C (Scheme 19).[79] Once again, DHβC **78** was prepared by the BNR. Treatment of DHβC **78** under Noyori's asymmetric CTH conditions furnished THβC **79** in good yield and in good enantioselectivity. The THβC **79** could then be taken through a 5-step reaction sequence, to give (-)-arborescidine C in a straightforward approach. Also, (+)-arborescidine A and (-)-arborescidine B was prepared in an analogous fashion during the same study.



Scheme 19. Total synthesis of (-)-arborescidine C by use of Noyori's asymmetric CTH protocol

3.1.4. Meyers' formamidine carbanion chemistry

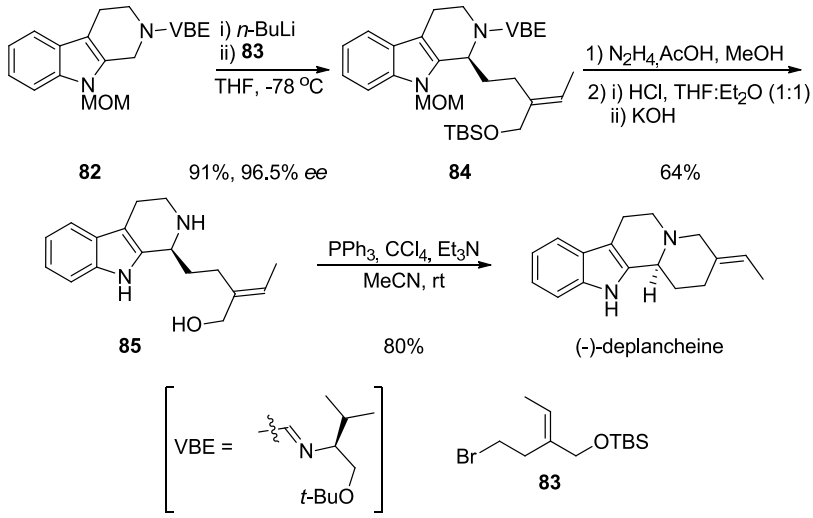
An attractive reaction in organic synthesis is the direct functionalization of the α-position to an amine.[80] One such methodology was developed by Meyers, who activated the α-position, by introducing a formamidine group on the amine, making it more susceptible to metalation by strong lithium bases.[81] By quenching the lithiated formamidine with a suitable electrophile, a facile C-C bond forming reaction was achieved. The reaction scope was explored and soon extended to include C-1 functionalization of tryptolines (for the structure of tryptoline see Figure 2A).[82] Formamidine **80**, synthesized from tryptoline in two steps, underwent metalation upon treatment with *t*-BuLi. Quenching the reaction with various electrophiles gave C-1 substituted THβCs **81** in good yields (Scheme 20).



Scheme 20. Concept of Meyers' formamidine chemistry in the synthesis of THβCs. E = electrophile

It did not take long until Meyers extended the reaction scope even further enabling the reaction to be performed in an asymmetric fashion. The asymmetric formamidine protocol, using chiral auxiliaries, was also extended towards the THβCs. The first example was in the total synthesis of (-)-deplancheine (Scheme 21).[83] By lithiating the

chiral formamidine **82**, derived from tryptoline and L-valine, with n-BuLi and quenching the reaction with electrophile **83**, TH*β*C **84** was obtained in 91% yield and an impressive 96.5% *ee*. Formamidine cleavage mediated by hydrazine in MeOH and AcOH followed by TBS group cleavage and methoxymethyl group removal gave TH*β*C **85** in 64% yield. The synthesis was completed by subjecting **85** to an Appel reaction giving (-)-deplancheine in 80% yield.

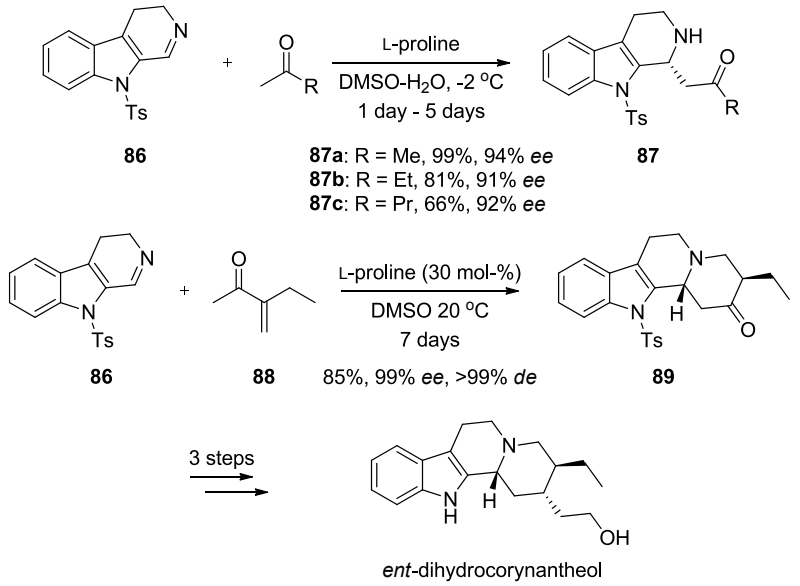


Scheme 21. Meyers' total synthesis of (-)-deplancheine

3.1.5. Nucleophilic addition to DH*β*Cs and *β*Cs

The last examples of asymmetric TH*β*C synthesis will be on the addition of carbon nucleophiles to DH*β*Cs. Early, achiral, examples of this particular approach include a Barbier type reaction of alkyl halides with DH*β*Cs mediated by zinc,[84] an aza-Diels-Alder reaction of DH*β*Cs in the presence of methyl pentadienoate,[85] addition of Grignard reagent to a BF_3 preactivated DH*β*C[86] and addition of 1-(trimethylsiloxy)-1,3-butadiene to an acyl iminium salt of a DH*β*C.[87] More recently, asymmetric versions have emerged. One of the first was the addition of allylzinc derivatives, in combination with a lithiated bis-oxazoline (BOX) ligand, to give two different DH*β*Cs in good yields and good enantioselectivity.[88] Another example is the proline catalyzed asymmetric addition of ketones and *α,β*-unsaturated ketones to DH*β*C by Itoh (Scheme 22).[89] Itoh and coworkers managed to obtain good yield and high enantioselectivities under the organocatalytic reaction conditions, albeit at long reaction times. He also managed to extend the protocol to the total synthesis of *ent*-dihydrocorynantheol. First tertacyclic ketone **89** was first obtained in a one-step reaction between DH*β*C **86** and *α,β*-unsaturated ketone **88**,

catalyzed by L-proline, Itoh synthesized tetracyclic ketone **89** in a remarkable enantioselectivity and diastereoselectivity. Elegant as the reaction was they were however unable to determine if the reaction proceeded *via* a Mannich-Michael or a hetero-Diels-Alder pathway. *ent*-Dihydrocorynantheol was obtained after three further reaction steps.

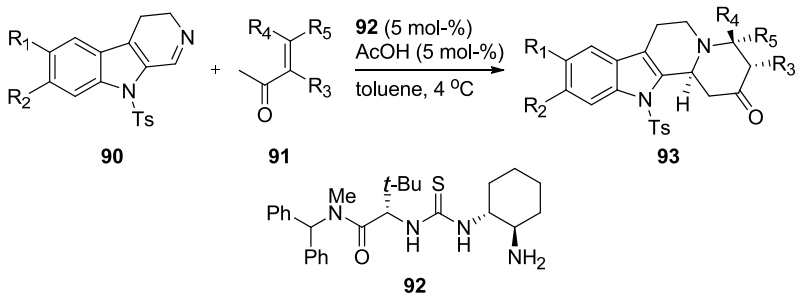


Scheme 22. Itoh's proline catalyzed synthesis of TH*β*C. Total synthesis of *ent*-dihydrocorynantheol

One of the most recent examples of the asymmetric nucleophilic addition to DH*β*C was reported by Jacobsen in 2013, which in principle is an extension of the work of Itoh. Jacobsen and coworkers employed an organocatalytic formal aza-Diels-Alder reaction catalyzed by a chiral primary aminothiourea organocatalyst **92** to gain access to a range of tetracyclic TH*β*Cs **93** (Scheme 23).[90] Generally excellent yields were obtained, and the reaction was shown to tolerate a range of substituents, mainly on R_5, with reaction times ranging between 30 h – 8 days. Excellent *ee*'s were obtained and in most cases also high dr's.

As a last example a close cousin to the above mentioned reaction, *i.e.* the analogous addition of nucleophiles to *β*Cs, will be briefly mentioned. The procedure was demonstrated in an asymmetric fashion by Ohsawa who installed an L-proline derived chiral auxiliary on the indole N-1 position and subsequently treated the *β*C with allyl stannane together with a chloroformate activating group to give the corresponding 1,2-

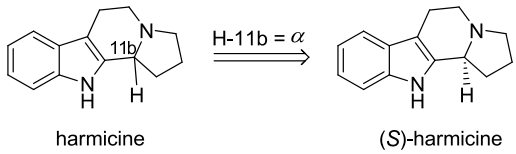
DHβC in good enantioselectivity (see chapter 3.2). Reduction of the 3,4-double bond then gave a allylated THβC.[91]



Scheme 23. Jacobsen's organocatalytic formal aza-Diels-Alder reaction. R_1 = H, Cl; R_2 = H, OMe; R_3 = H, Et; R_4 = H, Me; R_5 = H, Met, *n*-Pr, *i*-Pr, *t*-Bu, Ph, 2-pyrryl, 4-pyridinyl, 2-furyl, 3-furyl, 2-thiophenyl, various Ar (electron donating and withdrawing)

3.2. Synthesis of harmicine

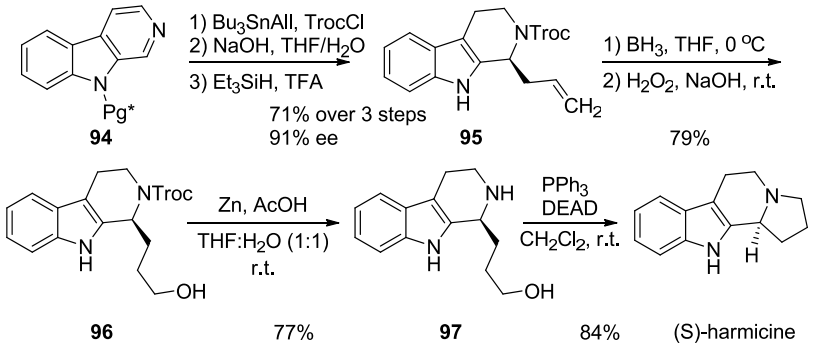
The story of harmicine is from many perspectives an interesting one, some of which will be disclosed in the following chapter. For a more thorough account on the history of harmicine and its applications, the reader is referred to manuscript I. Harmicine was first isolated from natural sources, *Kopsia griffithii*, in 1998. The novel tetracyclic structure was elucidated, and the basic ethanolic fraction from which the harmicine was isolated was also shown to possess anti-leishmania activity.[92] An interesting side note to this isolation is the peculiar statement regarding the absolute configuration of harmicine. The authors stated in the article that the presence of Wenkert-Bohlmann absorbtion bands in the IR spectrum of harmicine would indicate that H-11b must be in an α-alignment, which based on their chosen way of drawing the molecules must translate to an (*S*)-configuration according to the Cahn-Ingold-Prelog (CIP) priority rule system (Scheme 24).[93] Assigning absolute stereochemistry by the presence of the Wenkert-Bohlmann



Scheme 24. Harmicine and the originally proposed absolute configuration

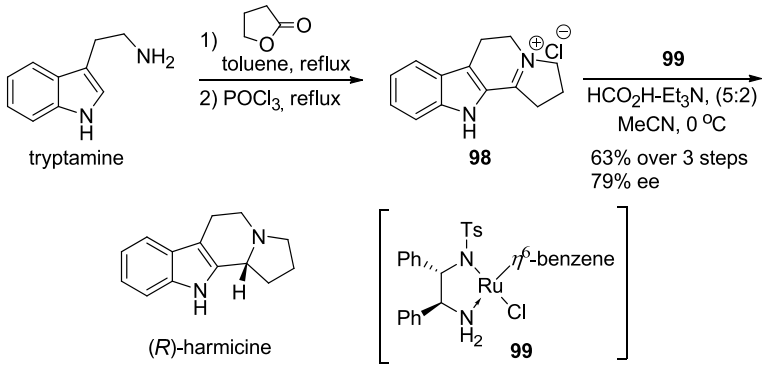
absorption bands, which of course are present in both the (*S*) and the (*R*)-stereoisomers, is erroneous – as is the use of the *α/β*-nomenclature in this case. Yet another interesting side note is that harmicine was first synthesized in racemic form already 42 years prior its isolation.[94]

In any case, the stereochemical assignment was taken literally in the first asymmetric total synthesis of harmicine, leading to the wrong enantiomer being synthesized.[95] In this first synthesis, Ohsawa treated *β*C **94**, carrying a chiral auxiliary at the indole N-1 position, with allylstannane in the presence of Troc-Cl,[91] giving a 1,2-DH*β*C, which was then subjected to removal of the chiral auxiliary and reduction of the 1,2-double bond to give TH*β*C **95**. Hydroboration followed by hydrogen peroxide oxidation gave alcohol **96**. Troc group removal, followed by cyclization under Mitsunobu conditions gave (*S*)-harmicine. Optical rotation measurement of the final product indicated that they had synthesized the enantiomer of natural harmicine.



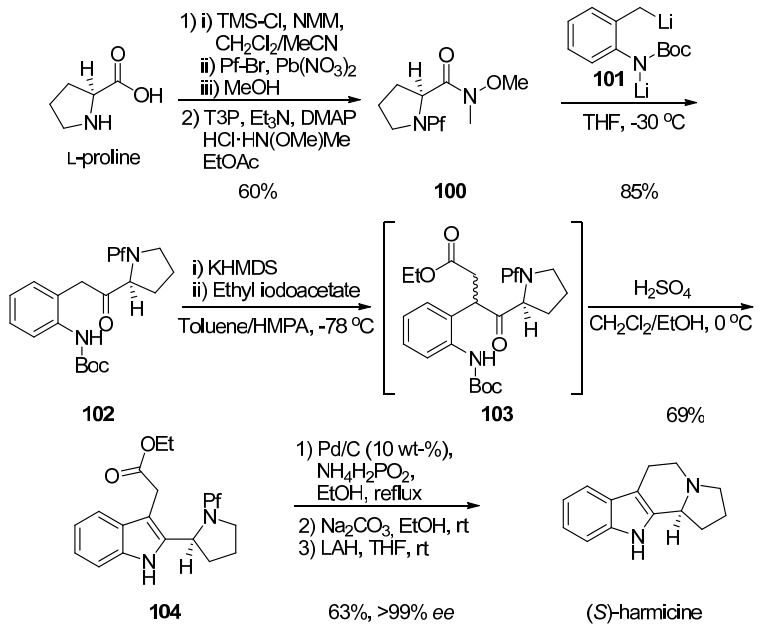
Scheme 25. Ohsawa's total synthesis of harmicine. Troc = 2,2,2-trichloroethoxycarbonyl; All = allyl; Pg* = (S)-N-(9-anthracenylmethyl)pyroglutaminyl

The first asymmetric synthesis of the naturally occurring enantiomer of harmicine can be attributed to Czarnocki.[96] Here the BNR was utilized in combination with the asymmetric Noyori transfer hydrogenation (Scheme 18) of the resulting iminium.[78] The short and straightforward synthesis started with preparation of the tetracyclic iminium salt **98**, by condensation between tryptamine and γ-butyrolactone followed by a BNR. The iminium salt was then reduced by the slightly modified Noyori type asymmetric CTH catalyst **99** in an azeotropic mixture of formic acid and Et_3N to give (*R*)-harmicine in 63% yield over 3 steps, albeit in a moderate *ee* of 79%.



Scheme 26. Czarnocki's total synthesis of the natural enantiomer of harmicine

Our interest in harmicine arose during our attempts to develop a novel route towards the THβC scaffold based on a chiral pool approach starting from amino acids. Aware of the inherent configurational instability of amino acid derived carbonyl compounds we opted to employ a Pf-protecting group strategy to maintain the stereochemical integrity of the chiral center (Figure 2B). This led us to explore the synthesis of harmicine starting from proline (Scheme 27).[II] Our synthesis started with proline which was Pf-protected under slightly modified literature conditions.[20] We found it necessary to replace Et_3N (pK_{aH} 10.75) with NMM (pK_{aH} 7.38) due to the observation of small amounts of racemization in the Pf-protection step, most likely taking place on the TMS-ester intermediate. Weinreb amide **100** was then obtained via a T3P® coupling of HCl·HN(OMe)Me, assisted by catalytic amounts of DMAP.[52] Lithiated Boc-*o*-toluidine **101**[97,98] was added to the Weinreb amide to give ketone **102** in good yield. Regioselective enolization, directed by the Pf-group, and quenching of the reaction with ethyl iodoacetate gave a 1:1 diastereomeric mixture of the 1,4-dicarbonyl **103**. Direct treatment of the mixture after an aqueous work up with acid facilitated Boc-group removal with sequential indolization to give indole **104**. The next step, Pf-group removal, proved more cumbersome than first anticipated. Hydrogenolysis under standard conditions, using Pd/C and H_2(g), failed to give any conversion. Turning to CTH conditions and performing a scan of hydrogen sources revealed Pd/C in combination with $NH_4H_2PO_2$ as a suitable system. Pf-group cleavage under these CTH conditions followed by C-ring closure and reduction of the intermediate lactam with LAH furnished harmicine. The reaction sequence was optimized, eliminating all silica gel chromatography purification, and scaled up to give >1 gram of enantiopure harmicine. Both (*S*) and (*R*)-harmicine was synthesized from L- and D-proline, respectively.



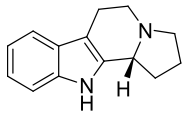
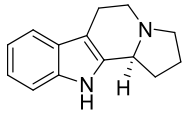
Scheme 27. Synthesis of harmicine developed in the course of this work

Recently harmicine was attributed to possess potent antinociceptive properties. [99] The mechanism of its action was however not made completely clear, however preliminary evidence pointed away from the opioid receptor regulating pain system. The same study also indicated that harmicine did not seem to act via an anti-inflammatory pathway. The study did not include any information regarding harmicine's activity towards the cannabinoid receptor system (CB_1 and CB_2), which prompted us to evaluate if such interaction might be responsible for the perceived antinociceptive effect.[100] The results are summarized in Table 2. Non-natural (*S*)-harmicine showed very weak agonist affinity towards both CB_1 and CB_2, while (*R*)-harmicine showed no activity. It is interesting to note that there is some selectivity preference on the absolute configuration of harmicine towards the cannabinoid receptors. However, these results are more a curiosity since the low affinity could not serve to explain harmicine's antinociceptive properties *via* the endocannabinoid system.[101]

Important features of the synthesis presented above includes the modified Pf-protection, the T3P mediated amide coupling and the CTH hydrogenolysis cleavage of the Pf-group (to our knowledge it is the first reported Pf-group removal under CTH conditions). Moreover, the chromatography free nature of the synthesis leading to gram amounts of harmicine and the complete retention in configuration at the α-amino carbonyl

stereocenter, especially during the lateral lithiation and during the enolazation reactions makes the synthesis an attractive alternative to existing protocols.

Table 2. Affinity of harmicine towards cannabinoid receptors (CB_1 and CB_2)

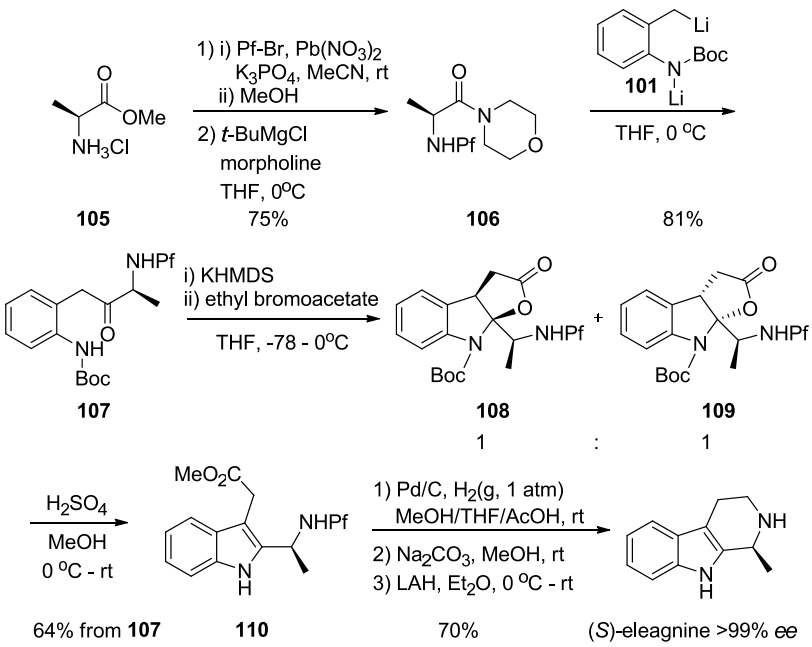
Compound	CB_1 agonist activity[a]	CB_1 antagonist activity[a]	CB_2 agonist activity[b]
	[^{35}S]GTPγS binding [%][c]	[^{35}S]GTPγS binding [% HU-210-evoked response][c]	[^{35}S]GTPγS binding [%][c]
 (*R*)-harmicine (10μM)	101	100	108
 (*S*)-harmicine (10 μM)	133	105	121
HU-210[d]	449 (10 nM)	-	174 (1 μM)
AM-251[e] (1 μM)	84	37	-
SR-144,528[f] (1 μM)	-	-	54

[a] rat cerebellar membranes; [b] hCB$_2$-CHO cell membrane; [c] mean value [d] cannabinoid receptor (CB_1 and CB_2) full agonist; [e] cannabinoid receptor (CB_1) antagonist/inverse agonist; [f] cannabinoid receptor (CB_2) antagonist/inverse agonist

3.3. Synthesis of eleagnine

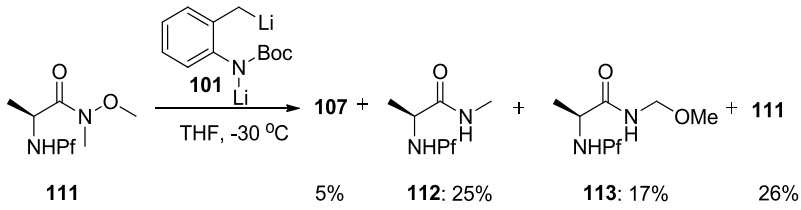
The harmicine study was further extended to the synthesis of (*S*)-eleagnine.[III] Eleagnine, a member of the simple TH*β*Cs, was originally isolated in its racemic form in 1950 from *Elaeagnus angustifolia*, and has since then also been found from various other plant sources.[57,102] Recently, the alkaloids have also been identified in common food stuff, such as chocolate and soy sauce.[103] The route, a modified version of the harmicine synthesis, started with the Pf-protection of commercially available methyl ester **105**. By use of the methyl ester, no *in situ* TMS protection of the carboxylic acid was necessary, simplifying

the reaction procedure in a practical aspect. The corresponding proline methyl ester could also be Pf-protected using the same procedure, however a slight drop in *ee* was observed.[II] Morpholine amide **106** was prepared, which represents a cheaper albeit less reactive option to the more commonly used Weinreb amides (Scheme 28).[104] The amide switch was made due to the observation of decomposition of Weinreb amide **111** upon treatment with dilithiated *N*-Boc-*o*-toluidine **101**, leading to low yields of the desired product **107** and the isolation of byproducts **112** and **113** (Scheme 29). We attributed the reaction outcome of Weinreb amide **111** to the free *N*-H proton leading to quenching of the nucleophile **101**, subsequently resulting in decomposition *via* an intramolecular pathway by proton abstraction from either the *N*-Me or the *N*-OMe group. Analogous decomposition of Weinreb amides have been observed on a number of occasions.[105] Morpholine amide **106**, lacking the possibility to decompose in the same fashion as the Weinreb amides, was therefore introduced. Treatment of compound amide **106** with dilithiated Boc-*o*-toluidine **101** satisfyingly gave ketone **107** in good yield. The next surprise came during the addition of ethyl bromoacetate to the potassium enolate of ketone **107**, when the tricyclic γ-lactones **108** and **109** were obtained. The diastereomeric ratio of **108** and **109** at 0 °C was determined to be 1:1 by NMR. The ratio could be improved to 6:1 (**108**:**109**) by lowering the reaction temperature to -78 °C, although at a cost in the isolated yield of **108**, 45%. The diastereomeric ratio of **108** and **109** was however of no consequence, so the 1:1 mixture of lactones **108** and **109** was treated with



Scheme 28. Synthesis of (*S*)-eleagnine developed in the course of this work

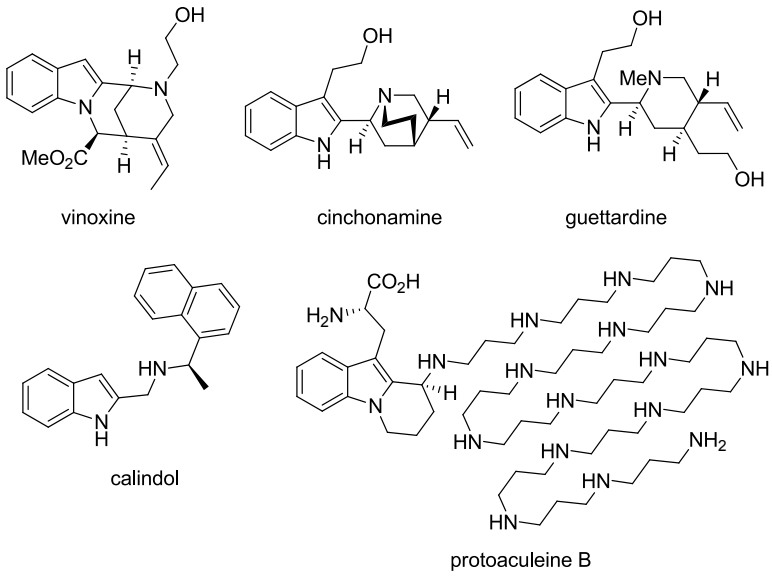
methanolic sulfuric acid, to facilitate sequential Boc-group cleavage, indolization and methyl esterification giving indole **110**. Pf-group removal followed by C-ring formation and reduction of the intermediate amide gave (*S*)-eleagnine in >99% *ee*, as confirmed by enantioselective HPLC analysis. The sequence could easily be scaled up to gram quantities, giving 1.4 g of enantiopure (*S*)-eleagnine in one batch. The synthesis illustrates that the presented strategy towards TH*β*C can be applied on a broader range of amino acid substrates, as will be further presented in the following chapter.[IV]



Scheme 29. Decomposition of Weinreb amide **111**. Reaction conditions: **111** (100 mol-%) was treated with **101** (110 mol-%) at -30 °C. The reaction was stirred for 1 h. Isolated yields after silica gel chromatography.

3.4. Synthesis of 2-indolyl methanamines

A group of compounds structurally related to the TH*β*Cs is the 2-indolyl methanamines, which contain all the same structural features with the exception of the ethenyl-bridge connecting the C-ring nitrogen and the indole C-3 position. Despite the close resemblance, reports of such compounds in the literature are scarce. Only one natural product carrying the 2-indolyl methanamine framework with an unsubstituted indole C-3 position, vinoxine,[106] has been isolated to date. However, some other closely related compounds of interest do exist as exemplified by calindol, a synthetic 2-indolyl methanamine with high affinity towards the calcium sensing receptor, [107] and the natural products cinchonamine,[108] guettardine[109] and protoaculeine B[110] (Scheme 30). A unifying factor for the aforementioned compounds is that they are not accessible *via* conventional TH*β*C methods (*vide supra*). We therefore found it appropriate to expand the scope of the TH*β*C synthesis methodology described in the previous chapters, to also include 2-indolyl methanamines.[IV] A few examples of the synthesis of chiral 2-indolyl methanamines do exist in the literature, including the following: resolution of hydroxyureas, [111] diastereoselective addition of 2-lithiated indoles to either hydrazones[112] or imines[113] carrying a chiral directing group, Pd catalyzed Sonogashira/cyclization of chiral propargylamines and 2-iodo anilines,[114] enantioselective chiral phosphoric acid catalyzed Friedel-Crafts/oxidation protocol[115] and finally a three component domino reaction of 2-ethynylanilines, aldehydes and secondary amines – catalyzed by Cu(I)[116].

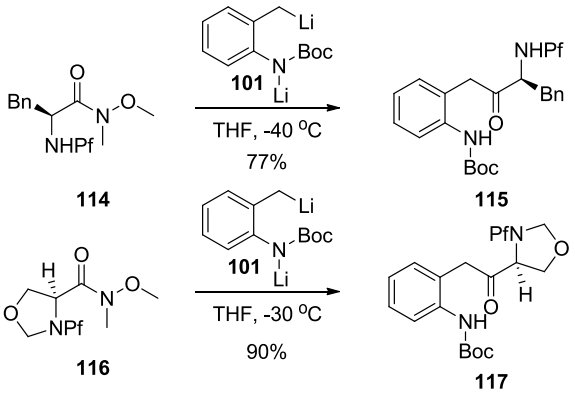


Scheme 30. Examples of 2-indolyl methanamines

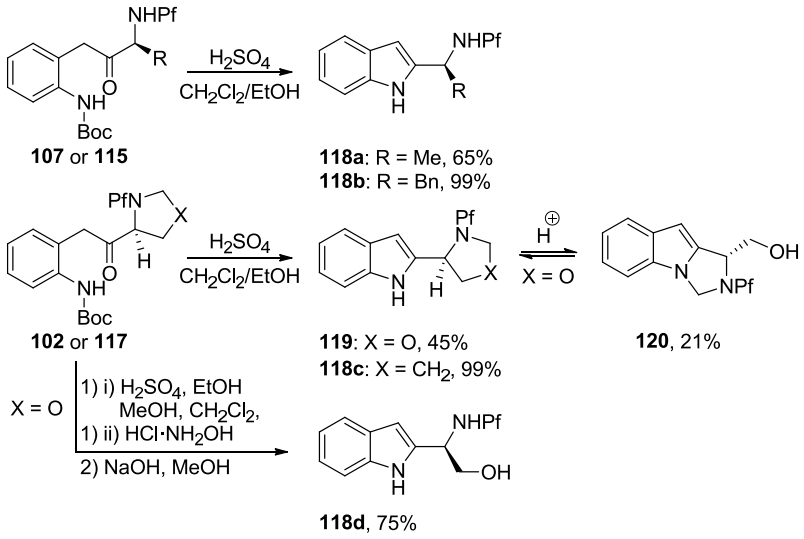
Four amino acids were selected as suitable starting material in the 2-indolyl methanamine synthesis, and chosen on the basis of gaining a large structural diversity. Ketones **102**[II] and **107**[III] was prepared as previously described and ketones **115** and **117** were prepared in an analogous fashion (Scheme 31). The corresponding morpholine amide of the phenylalanine derived Weinreb amide **114** proved too unreactive in the lateral lithiation, most likely due to the added steric bulk of the phenyl group. However, the decomposition pattern observed for Weinreb amide **111** (Scheme 29), was not observed for Weinreb amide **114**, despite the presence of a free *N*-H proton. Performing a reaction temperature optimization for the lateral lithiation of Weinreb amide **114** we found that a good yield of 77% could be obtained at -40 °C.

With the ketones **102, 107, 115** and **117** in hand, the Boc-group cleavage/indolization was studied. Ketones **102**, **107** and **115** underwent smooth reaction in ethanolic sulfuric acid, using CH_2Cl_2 as a co-solvent, giving indoles **118a-c**. However, the reaction of ketone **117** proved to be slightly more complicated. Treatment of ketone **117** under the same reaction conditions only partially cleaved the Boc-group, which led to low yields of indole **119**. Also a rearrangement of the methylene group to indole aminal **120** was observed under the acidic reaction conditions. In order to bypass these problems, treatment of ketone **117** under less acidic conditions, leaving the Boc group intact and preventing the formation of aminal **120**, followed by aminal cleavage using hydroxyl amine and telescoping the

reaction further by performing the indole-Boc cleavage under basic conditions furnished the desired indole **118d**.



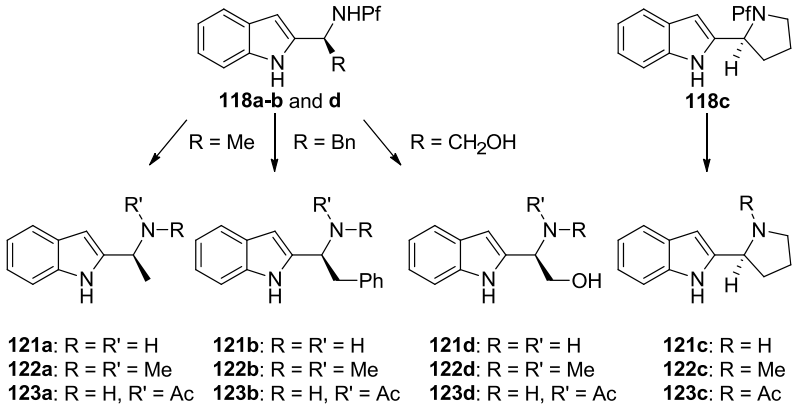
Scheme 31. Synthesis of ketones **115** and **117**



Scheme 32. Indolization of ketones **102, 107, 115** and **117**

The Pf-protected 2-indolyl methanamines were then deprotected by Pd/C catalyzed hydrogenolysis, acylated (by either Ac_2O or AcCl) and methylated by reductive amination (using formaldehyde and $NaBH(OAc)_3$) [117] to provide a small library of

compounds (Scheme 33). The enantiopurity was once again determined to be at least 99% *ee* for all reported 2-indolyl methanamines.



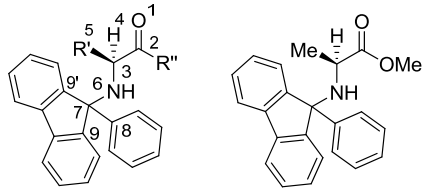
Scheme 33. 2-indolyl methanamines synthesized.

4. Conformational study of Pf-protected *α*-amino carbonyl compounds

As stated in Chapter 2.1, the mechanism by which the Pf-group manages to maintain the stereochemical integrity of *α*-amino derivatives under strongly basic reaction conditions has not been fully elucidated. Prior to this work no thorough studies had yet to be undertaken, which prompted us to investigate the phenomenon, by X-ray crystallographic measurements, DFT calculations and NMR data.

4.1. Computational study

We started by trying to reproduce the MM calculations which had placed the H(4) (for atom numbering see Figure 4) antiperiplanar (or alternatively periplanar) to the C(2)-O(1) double bond.[24] A simple substrate, methyl ester **124**, was chosen as a model compound upon which the calculations were subsequently performed. By performing a conformational search, applying the MM2*[118] and MM3*[119] force fields we were able to satisfactorily reproduce the aforementioned results (Table 3). However, when doing a small force field scan, employing also MMFF[120] (and MMFFs) and OPLS-2005,[121] a clear variation in the data output could be observed. This variation puts the previously postulated stereoelectronic effects under question. We proceeded by refining the OPLS-2005 conformational search by quantum mechanical (QM) density functional theory (DFT) calculations at the M06-2X/6-31G**++ level of theory.[122] The global minimum was found to attain a H(4)-C(3)-C(2)-O(1) dihedral angle of -162 ° (entry 5, conformer 1, Table 3).



124

Figure 4. Generic Pf-protected *α*-amino carbonyl compound and **124**. Numbering (does not follow IUPAC guidelines) of relevant atoms to simplify the conformational (computational and crystallographic) discussion.

Table 3. Molecular mechanics conformational search on **124**, showing data for the 5 lowest energy conformations[a]

Entry	Force Field	Conformer	Dihedral angle[b] [°]	Energy[c] [kJ/mol]	Population distribution[d] [%]
1	MM2*	1	-177	0	84.5
		2	2	5.0	11.3
		3	-150	8.9	2.3
		4	32	12.3	0.6
		5	119	13.8	0.3
2	MM3*	1	179	0	87.4
		2	13	7.1	5.0
		3	38	8.1	3.4
		4	170	10.2	1.4
		5	26	10.2	1.4
3	MMFF[e]	1	-155	0	92.7
		2	-148	8.6	2.8
		3	34	9.3	2.2
		4	27	9.8	1.8
		5	-167	13.1	0.5
4	OPLS-2005	1	10	0	35.4
		2	-139	0.4	29.8
		3	-155	2.6	12.4
		4	-143	3.1	10.1
		5	16	6.3	2.8
5	OPLS-2005 (QM-refined)[f]	1	-162	0	69.6
		2	-151	4.5	11.2
		3	19	4.7	10.5
		4	35	5.6	7.4
		5	16	12.0	0.5

[a] MM calculations performed in gas phase using MacroModel 10.0, without any constraints; electrostatic treatment was set to constant dielectric; [b] Dihedral angle between H(4)-C(3)-C(2)-O(1); [c] Relative potential energy; [d] Determined as the Boltzmann distribution at T = 298.15 K; [e] MMFFs gave identical results; [f] Calculations performed in gas phase using Jaguar 8.0; theory: DFT (M06-2X) with the basis set 6-31G**++.

The calculated lowest energy conformation of **124** was also largely supported by crystallographic data of the same compound (Figure 5).

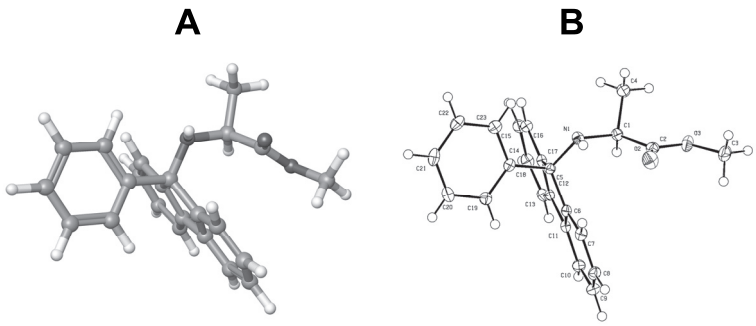


Figure 5. A: Lowest calculated energy conformation of **124**; B: crystal structure of **124**

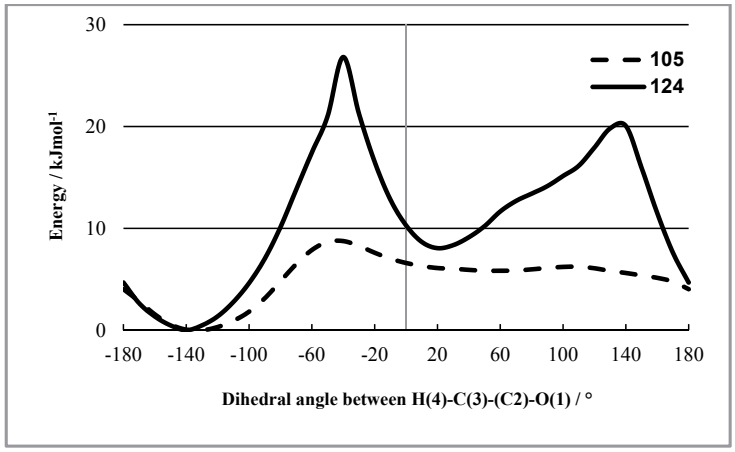


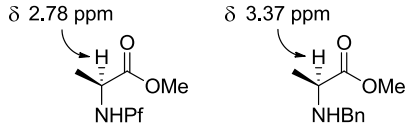
Figure 6. Coordinate scan of **105** and **124**, rotation around the C(2)-C(3) bond in 10º increments. Calculations performed in gas phase using Jaguar 8.0; theory: DFT(B3LYP) with the basis set 6-31G**. Energy: relative total electronic energy.

At this stage we found it relevant to examine the rotational barrier around the C(2)-C(3) bond. The lowest energy conformation of **124** was thus subjected to a coordinate scan wherein the abovementioned bond was rotated in 10 ° increments. The calculations were performed at the B3LYP/6-31G** level of theory (Figure 6).[123] Next, the same calculation sequence was also performed on alanine methyl ester **105**. Not surprisingly, the bulky Pf-group on **124** added a significant amount of torsional strain to the system when comparing to the free base of methyl ester **105**; however, the energy barriers are not as high as anticipated. The observed energy barrier is mostly an effect of the amino acid side chain being forced into close proximity of the Pf-group. Only 7 kJ/mol (1.7 kcal/mol) of energy is required to forcibly align the H(4) σ-sigma orbital with the π*-orbital of the

carbonyl double bond, making a deprotonation reaction a feasible event. However, worth mentioning is that H(4) is kept, all through the coordination scan, dead center over the fluorenyl ring system, possibly imposing large enough steric shielding to prevent deprotonation from occurring.

4.2. NMR

The close proximity of the H(4) to the Pf-ring system was also observed in solution by the use of NMR spectroscopy. The chemical shift of H(4) (δ 2.78)[124] can be compared with the corresponding proton in *N*-Bn-alanine methyl ester **125** (δ 3.37), indication a strong shielding effect on H(4) invoked by anisotropic effect of the Pf-ring system. A NOESY coupling between H(4) and the Pf-group in **124** was also observed.

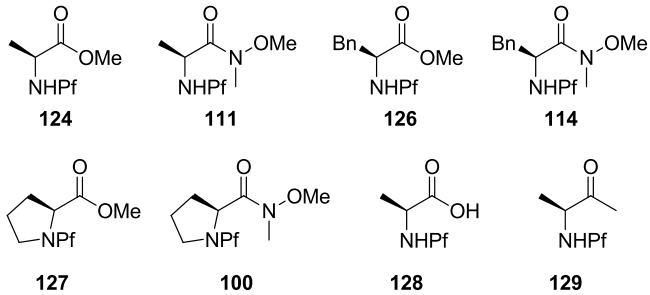


124 **125**

Figure 7. Chemical shifts of the α-hydrogens in amino esters **124** and **125**

4.3. Crystallographic data

During the course of the above mentioned investigations (chapter 3.2, 3.3 and 3.4) a number of crystalline *N*-Pf *α*-amino carbonyl compounds were isolated, mounting out to eight X-ray crystal structures being obtained (Figure 8, Table 4).



124 **111** **126** **114**

127 **100** **128** **129**

Figure 8. α-amino carbonyl compounds of which X-ray crystal structures were obtained

Some interesting trends can be observed from the crystal structure data. In all but one case, proline methyl ester **127**, H(4) is aligned on top of the fluorenyl ring system as

observed in the computational study. In **127**, however, H(4) is situated in the space between the Pf phenyl group and the fluorenyl group. It is also evident that the H(4)-C(3)-C(2)-O(1) dihedral angle in broad terms matches the calculated angle for methyl ester **124**. Furthermore, the H(4)-C(3) bond is syn-periplanar to the N(6)-C(7) bond, indicating a favorable conformation for a concerted E2 syn-elimination reaction. This orbital alignment might help explain the observed Pf-anion elimination from *N*-Pf-alaninal **5** under basic conditions (Scheme 3).[7]

Table 4. Dihedral angles from X-ray crystal structure data

Compound	Dihedral angle [°] H(4)-C(3)-C(2)-O(1)	Dihedral angle [°] H(4)-C(3)-N(6)-C(7)	Dihedral angle [°] C(3)-N(6)-C(7)-C(8)
124	-120	5	-175
111	-147	23	172
128 [a]	19/23 (44/45)[b]	-12.5/-24 (19/15)	178/178 (179/177)
129	-149	26	177
126	-153	31	176
114 [c]	-153/-150	29/32	-177/179
127	-149	3	61
100	-161	28	174

[a] Structure data contains four crystallographically independent molecules, two in the NH/COOH state and two in the NH_2^+/COO^- state (zwitterionic forms shown in brackets); [b] Angle between only one of the carboxylates oxygens presented; [c] Structure data contains two crystallographically independent molecules.

4.4. Conclusions

The calculated rotational barrier about the C(3)-C(2) bond in *N*-Pf alanine methyl ester **124** is too low to simplify the mechanism behind the stereochemical protecting effect through such an argument. However, it is obvious that H(4) is kept in close proximity to the Pf fluorenyl ring system, causing at the very least a significant amounts of steric shielding, which most likely leads to a certain hampering of a deprotonation/reprotonation pathway. Furthermore, as already speculated by Rapoport, it might be a cause to assume that a Pf-elimination pathway is favored over the enolization pathway due to the periplanar alignment of the H(4)-C(3) and the N(6)-C(7) bonds.[7] To summarize, after computational conformation analysis coupled with NMR data and X-ray crystal data we have not found any hard evidence supporting the previously proposed stereoelectronic argument regarding the stability of *N*-Pf protected α-amino carbonyl derivatives. It is important to note that the discussion herein does not take into account

the possible increased energy barrier the Pf-group might induce in the enolization transition state, when the sp^3 carbon rehybridizes to sp^2, originating from the extra allylic strain the Pf-group might impose upon the system. To further probe such effects more rigorous calculations would be necessary.

5. General conclusions

The work presented in this thesis describes a novel synthetic strategy towards C-1 substituted chiral TH*β*Cs by use of a chiral pool strategy, starting from amino acids. The amino acid side chain was shown to be efficiently transferred through the reaction sequence to the final products with full retention of stereochemical information. A Pf-protecting group strategy was employed to protect the vulnerable stereocenter on the *α*-amino carbonyl derivatives from racemization. The strategy culminated in the synthesis of two bioactive TH*β*C natural products in gram quantities, without any erosion of the optical purity (*ee* ≥ 99%) of the amino acid starting material, *via* the novel route.

The strategy was also extended to include a class of compounds underrepresented in the literature – the 2-indolyl methanamines. The compound class, unobtainable by conventional TH*β*C synthetic methodologies, *i.e.* PSR and BNR, was readily synthesized by the Pf-protecting group/chiral pool strategy. A small library of 2-indolyl methanamines, starting from 4 structurally different amino acids, was synthesized.

The results presented herein shows that the TH*β*C compound class is readily obtained from the described amino acid chiral pool strategy, and that the methodology offers a good alternative to traditional TH*β*C synthesis.

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